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**REVIEW ARTICLE**

# Use of molecular biomarkers in the early diagnosis and progression of endometriosis

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## ABSTRACT

**Introduction:** endometriosis is a chronic inflammatory disorder that affects quality of life and fertility. Conventional diagnosis requires invasive methods, representing a significant clinical challenge.
**Objective:** to evaluate the potential of molecular biomarkers to improve early diagnosis and monitoring of endometriosis, reducing reliance on invasive procedures.
**Methods:** a systematic review of the scientific literature was conducted across multiple databases, using an algorithm with keywords and Boolean operators to identify relevant sources. Selected studies, after applying rigorous inclusion and exclusion criteria, were critically assessed for timeliness, methodological quality, and thematic relevance, and coherently integrated into the final synthesis of the review.
**Development:** the literature identifies promising biomarkers, such as HE4 protein and microRNA panels (miR-200, miR-199a), which outperform traditional markers like CA-125 in accuracy. Cytokines (IL-6) and growth factors, associated with the inflammation and angiogenesis characteristic of the disease, are also highlighted. Underlying epigenetic and genetic mechanisms offer perspectives for the development of personalized therapies.
**Conclusions:** molecular biomarkers represent a valuable tool for less invasive diagnosis and more effective monitoring. However, validation in diverse populations and a deeper understanding of pathophysiological mechanisms are required for widespread clinical implementation and the development of targeted treatments.

**Keywords:** Biomarkers; Diagnosis; Endometriosis; Clinical Evolution.

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## INTRODUCTION

Pelvic endometriosis is a chronic inflammatory syndrome related to endometrial tissue that migrates into the abdominal cavity. It causes chronic pelvic pain and can lead to infertility. Mechanisms such as epigenetic abnormalities and genetic mutations contribute to its development. The associated pain varies widely: some lesions are asymptomatic, while others trigger neuroinflammation.[1]

According to Christina López, a gynecology specialist at Los Valles Hospital in Ecuador, approximately one in ten women in the country suffers from endometriosis. In 2016, 1,112 new cases were identified, while in the following year, 2017, the number decreased to 1,027. Importantly, more than half of these women sought medical care only for routine checkups and not necessarily due to suspicion of the disease.[2]

This painful condition affects not only physical health but also mental well-being and patients' quality of life. It is recognized that social stigma can have adverse effects on individuals living with chronic illnesses, including endometriosis, contributing to social exclusion, high stress levels, and difficulties accessing healthcare.[3] During reproductive age, endometriosis causes more pronounced symptoms. Significant advances have been made in its management, encompassing diagnosis, pain treatment, fertility care, and the identification and treatment of comorbid conditions.[4]

Pelvic pain—particularly before or during menstruation—is the primary symptom. Other symptoms include pain during intercourse, difficulty urinating or defecating, gastrointestinal symptoms, and bladder issues. These symptoms may or may not be associated with infertility.[5]

Endometriosis can be diagnosed through various techniques: physical examination to identify nodules and tender areas, ultrasound for imaging, magnetic resonance imaging (MRI) for detailed visualization using magnetic fields, laparoscopy for surgical abdominal exploration, advanced endoscopy for lesion visualization and treatment, and emerging technologies such as artificial intelligence for medical image analysis. Additionally, biomarkers in bodily fluids such as blood are being investigated to improve diagnostic accuracy and disease monitoring.[6] However, clinical diagnosis remains challenging, as symptoms of endometriosis may resemble or overlap with those of other gynecological or non-gynecological conditions causing pelvic pain.[7]

In recent years, numerous studies have aimed to identify an effective, non-invasive diagnostic method for endometriosis, with molecular biomarkers emerging as one such approach.[8] A biomarker is a molecular messenger found in blood, bodily fluids, and tissues that conveys information about health or disease status. As a unique biological signature for each individual, these markers provide insights into normal or abnormal physiological processes. Currently, biomarkers are used to predict disease and assess treatment effectiveness.[9] In endometriosis, serum biomarkers have traditionally been used, but they have limitations because they can be altered in other conditions affecting the ovaries and peritoneum. Recently, more effective biomarkers have been developed for diagnosis and treatment.[7]

In light of the above, the present bibliographic review was conducted with the objective of evaluating the potential of molecular biomarkers to improve early diagnosis and monitoring of endometriosis, thereby reducing dependence on invasive procedures.

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## METHODS

This study is a systematic bibliographic review designed to synthesize the available scientific evidence on molecular biomarkers in endometriosis. The search strategy was carried out between January and March 2024, encompassing articles published from 2013 to 2023 to ensure current and relevant information.

Information sources included the electronic databases PubMed, Scopus, Web of Science, and the academic search engine Google Scholar. Additionally, reference lists of selected articles were examined to identify relevant literature not initially captured. The search strategy employed Boolean operators (AND, OR) and key terms in Spanish and English, such as: "endometriosis," "molecular biomarkers," "early diagnosis," "microRNA," "CA-125," and "HE4."

Inclusion and exclusion criteria were established to refine results. Included were original articles and reviews published in English or Spanish that directly addressed the use of biomarkers in the diagnosis or monitoring of endometriosis in humans. Excluded were animal studies, duplicates, articles without full-text access, publications prior to 2013, and those not directly related to the main topic.

The selection process followed PRISMA guidelines. Initially, 850 records were identified. After removing duplicates and screening titles and abstracts, 65 articles were selected for full-text evaluation. Finally, 22 studies met all criteria and were included in the synthesis.

Data extraction was performed systematically, collecting information on author, year, study design, population, biomarkers assessed, and main findings. Analysis focused on a narrative qualitative synthesis, grouping evidence by biomarker type (proteins, miRNAs, cytokines) and clinical application (diagnosis, prognosis).

## DEVELOPMENT

Pelvic endometriosis is recognized as a chronic inflammatory disorder characterized by the presence of endometrial tissue outside the uterine cavity, leading to pelvic pain, dysmenorrhea, dyspareunia, and often infertility.[5] Its etiology is multifactorial, involving mechanisms such as retrograde menstruation, genetic factors, and epigenetic alterations that promote the implantation and proliferation of endometrial cells in ectopic locations.[10,11]

This condition not only affects physical health but also carries a significant psychological burden, exacerbated by social stigma and difficulties in accessing timely diagnosis.[2] Traditionally, diagnostic confirmation has relied on invasive procedures such as laparoscopy, which has driven the search for less invasive alternatives, among which molecular biomarkers stand out.[6]

In this context, molecular biomarkers emerge as promising tools for early diagnosis and disease monitoring.[12] They are defined as measurable biological indicators that reflect physiological or pathological processes. In endometriosis, they can be classified as diagnostic, prognostic, or therapeutic response biomarkers.[13]

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Among the most studied are circulating proteins such as CA-125 and HE4. Although CA-125 is widely used, it has important limitations: a meta-analysis by Mol BW et al.,[14] reported a sensitivity of only 52 % and a specificity of 93 %, with greater utility in advanced disease stages. In contrast, HE4 has demonstrated superior performance in studies such as that by Scaletta G et al.,[15] showing higher sensitivity and specificity—particularly when combined with other markers—suggesting its potential for improved early-stage detection.

Beyond proteins, microRNAs (miRNAs) have gained prominence in recent research. Studies like that of Suryawanshi S et al.,[16] identified significantly elevated levels of miR-200 and miR-199a in the plasma of endometriosis patients, showing high sensitivity and specificity. Other investigations, such as Cosar E et al.,[17] have reported alterations in miR-21 and miR-451, proposing that a miRNA panel could enhance diagnostic accuracy. However, variability in results according to disease stage and study population necessitates broader validation before routine clinical implementation.

Concurrently, cytokines and growth factors associated with inflammatory and angiogenic responses—such as IL-6 and vascular endothelial growth factor (VEGF)—have been explored as complementary markers. Bedaiwy MA et al.,[18] observed elevated IL-6 levels in serum and peritoneal fluid, while McLaren J et al.,[19] highlighted VEGF's role in the angiogenesis of endometriotic implants; however, their specificity is limited by elevation in other inflammatory and angiogenic conditions.

Beyond diagnosis, monitoring endometriosis progression requires biomarkers that reflect the disease's biological activity. In this area, estrogen receptors (ERα and ERβ) have received attention: Han et al.,[11] reported significantly increased ERβ expression in endometriotic tissue, which could be used to assess response to hormonal therapies.[20]

Additionally, matrix metalloproteinases (MMPs)—involved in tissue invasion—have been proposed as progression indicators, as noted in studies like that of Bruner-Tran KL et al.,[21] Immunological markers such as C-reactive protein (CRP) have also shown correlation with disease severity, as indicated by Agic A et al.,[22] although their lack of specificity limits standalone use.

The integration of these findings reveals an evolving landscape in which the combination of multiple biomarkers (proteins, miRNAs, and inflammatory markers) appears to be the most promising approach to overcome the limitations of univariate strategies.[12,13] Nevertheless, significant challenges persist, including heterogeneity among studied populations, the influence of comorbidities, and a lack of standardization in detection methodologies.[7]

Moreover, most research has focused on women with advanced symptoms, leaving a gap in the identification of biomarkers for early-stage or asymptomatic forms of the disease.[6] These limitations underscore the need for longitudinal, multicenter studies to validate the clinical utility of biomarkers across diverse contexts.

Regarding underlying mechanisms, advances in genetics and epigenetics have provided valuable insights into endometriosis pathogenesis. Various studies have identified genetic loci associated with susceptibility,[10,20] while epigenetic alterations—such as DNA methylation—may explain part of the variability in gene expression related to proliferation and inflammation.[17] These findings not only deepen disease understanding but also open pathways for targeted therapies and personalized medicine strategies, representing a promising horizon for the comprehensive management of endometriosis.[5]

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## CONCLUSIONS

Endometriosis remains a gynecological disease of significant global impact, negatively affecting women's quality of life and fertility. Advances in molecular biomarkers offer new opportunities to improve early diagnosis, monitor disease progression, and evaluate treatment response. However, further research is needed to validate the efficacy and specificity of these biomarkers across diverse populations and clinical settings. Additionally, a deeper understanding of the molecular and genetic mechanisms involved is required to develop more targeted and personalized therapies.

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