IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Artificial Intelligence And Machine Learning In Endometriosis: Addressing Diagnostic Delay Through Data-Driven Precision Medicine

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Abstract

Endometriosis is an estrogen-dependent inflammatory condition that affects approximately 10% of reproductive-age women worldwide, or an estimated 190 million women. Although it has a high clinical and socioeconomic burden, the average latency to diagnosis is 7-11 years, which is intolerable for patients. The structural normalisation of severe pain during menstruation, a lack of provider awareness and a historical clinical preoccupation with laparoscopy are mostly responsible for this diagnostic delay. Failure to detect or misdiagnose this condition is compounded by extreme symptom variation and by a large overlap between gastrointestinal, urological and musculoskeletal disorders, such as irritable bowel syndrome, interstitial cystitis and low back pain. To overcome these systemic bottlenecks and the data fragmentation across many clinical repositories, the field is transitioning to artificial intelligence (AI) and machine learning (ML) architectures. This systematic review comprehensively assesses the use of computational systems that decode multi-modal, high-dimensional biomedical data streams for improved risk stratification and diagnostic optimisation. Supervised learning classification models, such as AdaBoost, Random Forests, and XGBoost, coupled with unique mobile health screening applications, have shown outstanding predictive capacity, achieving an area under the receiver operating characteristic curve (AUC) of 0.94 using patient-reported symptom patterns. At the same time, natural language processing (NLP) systems such as the context-aware transformer models (e.g., BERT) and longitudinal generative forecasting models (e.g., Foresight) are achieving unprecedented accuracy in extracting comprehensive phenotypic information, discovering complex networks of comorbidities, and identifying trends of misdiagnoses in the unstructured passages of the electronic health record (EHR) text. Further, innovative machine learning techniques are successfully leveraging non-invasive diagnostics to optimise automated analysis and categorisation of complex biomarker panels (circulating microRNAs and endometrial BCL-6 expression), and to improve pelvic imaging segmentation and accuracy on transvaginal ultrasound and magnetic resonance imaging systems, thereby eliminating unnecessary pre-surgical risks. Lastly, this analysis examines the use of explainable AI tools, such as LIME and SHAP, to demystify the inner workings of complex algorithms and foster vital physician trust, helping remove the "black box" hurdle. Finally, it is crucial to address variations across datasets arising from inconsistent patient recruitment mechanisms and to achieve universal semantic interoperability across different, global, and independent systems of terminology, such as the ICD and SNOMED-CT common ontologies, to enable equitable, objective, and person-centred gynaecological care worldwide.

Keywords: Endometriosis, Diagnostic Delay, Machine Learning, Natural Language Processing, Electronic Health Records, Multimodal Biomedical AI.

Review Methodology

The purpose of this review was to assess the current use of AI and ML technologies in the diagnosis and management of endometriosis, especially with the aim of minimizing the diagnostic delay and enhancing clinical decision making. The literature search was conducted using comprehensive search in electronic databases such as PubMed, Scopus, Web of Science, Google Scholar and ScienceDirect. The search strategy involved using keywords and combinations of keywords, including “endometriosis”, “artificial intelligence”, “machine learning”, “deep learning”, “natural language processing”, “electronic health records”, “biomarkers”, “diagnostic delay”, “medical imaging”, and “precision medicine”. Boolean operators (AND, OR) were employed to narrow and filter the search, yielding studies relevant to the use of AI in the study of endometriosis. The journal articles, systematic reviews, meta-analyses, clinical studies and conference publications were selected if they were published primarily in the period 2010 to 2025 and were peer-reviewed. Studies were chosen that are relevant to the application of AI in the diagnosis, prediction, discovery of biomarkers, imaging analysis, electronic health record analysis, and personalized treatment strategies of endometriosis. The exclusion of articles not relevant to endometriosis, studies without scientific evidence, duplicates and articles not published in English (where applicable). Selected literature was critically analyzed and organized into different thematic groups such as diagnostic challenges, symptom heterogeneity, biomarker-based diagnostics, imaging technologies, machine learning models, NLP systems, EAI, and future directions for precision medicine. The results were compiled to uncover the latest developments, challenges, and potential future prospects of integrating AI technologies into endometriosis treatment.

1. Introduction

Epidemiology

Endometriosis represents one of the most prevalent gynaecological disorders, affecting approximately 10% of women of reproductive age globally, with recent epidemiological studies indicating substantial regional variations in prevalence and diagnostic patterns (As-Sanie et al., 2025; Sarria-Santamera et al., 2021). This chronic inflammatory condition, characterised by the presence of endometrial-like tissue outside the uterus, imposes a significant clinical burden through its hallmark symptoms of chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility, affecting an estimated 190 million women worldwide (Xu et al., n.d.; Yan et al., 2025). The complexity of endometriosis extends beyond its primary manifestations, with emerging evidence demonstrating substantial comorbidity patterns, including strong associations with irritable bowel syndrome, interstitial cystitis, and various autoimmune conditions, creating a multisystem disorder that challenges traditional diagnostic approaches (Chiaffarino et al., 2021; Peters et al., 2022; Shigesi et al., 2025).

Clinical Burden

One of the most critical challenges in endometriosis management is the persistent diagnostic delay, averaging 7-10 years from symptom onset to definitive diagnosis, a phenomenon documented across diverse healthcare systems from the Netherlands to India (Wróbel et al., 2022; Devi et al., 2022). This diagnostic latency stems from multiple factors including symptom overlap with other conditions, normalization of menstrual pain, and the current gold standard requirement for laparoscopic visualization, which remains invasive and resource-intensive (Christ et al., 2021). The economic implications of endometriosis, with direct and indirect costs exceeding billions annually in healthcare systems worldwide, further underscore the urgency of developing more efficient diagnostic and treatment approaches (Soliman et al., 2018). Quality of life impacts are profound, with documented associations between endometriosis-related pain and decreased mental health, anxiety, and depression affecting millions of women globally (Facchin et al., 2015).

Heterogeneity in Symptoms and Pathology

The integration of artificial intelligence and machine learning technologies into endometriosis research and clinical practice represents a paradigm shift in addressing these longstanding challenges. AI/ML approaches demonstrate particular promise in handling the complex, multi-modal, high-dimensional biomedical data characteristic of endometriosis, including genomic profiles, imaging data, clinical symptoms, laboratory biomarkers, and patient-reported outcomes (Acosta et al., 2022; Sivajohan et al., 2022). Recent advances in multimodal biomedical AI have shown remarkable success in integrating diverse data types to improve diagnostic accuracy and treatment predictions across various medical domains, positioning these technologies as potentially transformative tools for endometriosis management (Luz & Lima, 2025). Machine learning algorithms have demonstrated efficacy in screening approaches, with studies showing improved accuracy in identifying endometriosis patients through analysis of symptom patterns, comorbidity profiles, and biomarker data (Bendifallah et al., 2022; Zhao et al., 2024). These technological innovations hold particular promise for addressing health disparities in endometriosis care, potentially democratizing access to specialized diagnostic capabilities and reducing the burden of expertise-dependent diagnosis (Rahmioglu & Zondervan, 2024).

Objectives of the Review This comprehensive analysis aims to systematically map the current landscape of artificial intelligence and machine learning applications in endometriosis research and clinical practice. The application of AI technologies in endometriosis research spans multiple domains, from diagnostic support systems that analyze complex symptom presentations to predictive models for treatment outcomes and fertility preservation strategies (Cetera et al., 2024). Recent evidence suggests that AI applications may also enhance our understanding of endometriosis pathogenesis through advanced data mining techniques applied to large-scale genomic and proteomic datasets, potentially identifying novel therapeutic targets and biomarkers (Brulport et al., 2024; Yong et al., 2021). Specifically, we examine AI/ML contributions to diagnostic accuracy improvement, treatment response prediction, biomarker discovery, and personalized medicine approaches. We evaluate the integration of multimodal data sources including genomic, proteomic, imaging, and clinical data in AI-driven endometriosis research platforms. Additionally, we assess the potential of these technologies to address current clinical challenges including diagnostic delay, treatment selection, and health disparities in endometriosis care. Finally, we identify key limitations, ethical considerations, and future research directions for AI/ML implementation in endometriosis management, with particular attention to validation requirements, clinical translation challenges, and the development of interpretable AI systems suitable for clinical decision support.

2. Symptom heterogeneity and overlap with other pelvic disorders

2.1 Challenges in Endometriosis Diagnosis and Management

Endometriosis research has gained considerable interest over the last decades. Despite growing interest, numerous challenges still remain, including the lack of universal diagnostic criteria, the difficulty of identifying a definite diagnosis due to the diverse symptomatology and diagnostic challenges, the ongoing normalisation of underlying endometriosis symptoms by both the health care provider and patient and many more (Marí-Alexandre et al., 2016; Lin & Yang, 2011); Wang et al., 2013). These factors contribute to a delay between the onset of first symptoms and a definite diagnosis, ultimately delaying effective treatment. The delay can have profound implications for patients, potentially worsening symptoms (Nezhat et al., 2022; Goncalves et al., 2021)
, impairing quality of life (Irungu et al., 2019; Monnaka et al., 2021)and increasing healthcare costs (Nezhat et al., 2022). As diagnostic delay appears to be a catalyst for many challenges in the field of endometriosis research, currently under investigation, reducing it is key.(De Corte et al., 2025)
The time to clinical diagnosis ranged from 0.3 to 8.6 years, indicating a considerable delay between the initial consultation with a healthcare provider and the receipt of a confirmed diagnosis. Contributing

factors may include misinterpretation of symptoms, symptom normalisation (Laganà et al., 2015), lack of access to specialised diagnostic tools or expertise(Leone Roberti Maggiore et al., 2016), healthcare system inefficiencies and diagnostic challenges due to complex or rare conditions (Laudanski et al., 2009; Li et al., 2025). The wide range of clinical times to diagnosis could further suggest disparities in healthcare infrastructure, resources and expertise across different regions and healthcare settings. Despite existing (inter-)national guidelines, healthcare systems and their qualities vary considerably between countries, and therefore, a more standardised approach is necessary in diagnosing endometriosis. (De Corte et al., 2025)

Diagnosis: Endometriosis can often present symptoms that mimic other conditions and contribute to a diagnostic delay. Ovarian endometrioma, adhesions and deep nodular forms of disease often require ultrasonography or magnetic resonance imaging (MRI) to detect. Histologic verification, usually following surgical/laparoscopic visualization, can be useful in confirming diagnosis, particularly for the most common superficial lesions. The need for histologic/laparoscopic confirmation should not prevent the commencement of empirical medical treatment. (World Health Organisation [WHO], n.d.)

Challenges and priorities: In many countries, the general public and most front-line healthcare providers are not aware that distressing and life-altering pelvic pain is not normal, leading to a normalisation and stigmatisation of symptoms and significant diagnostic delay. Patients who could benefit from medical symptomatic management are not always provided with treatments due to limited awareness of endometriosis among primary healthcare providers. Due to diagnostic delays, prompt access to available treatment methods, including non-steroidal analgesics (painkillers), oral contraceptives and progestin-based contraceptives, is often not achieved. Due to the limited capacity of health systems in many countries, access to specialised surgery for those who need it is sub-optimal. In addition, and especially in low and middle-income countries, there is a lack of multidisciplinary teams with the wide range of skills and equipment needed for the early diagnosis and effective treatment of endometriosis. Although primary health care professionals should play a role in screening and basic management of endometriosis, tools to screen and accurately predict patients and populations who are most likely to have the disease are lacking. In addition, many knowledge gaps exist, and there is a need for non-invasive diagnostic methods as well as medical treatments that do not prevent pregnancy.**(**World Health Organisation [WHO], n.d.)

Challenges in Diagnosis: Delay and Misdiagnosis: Diagnosing endometriosis presents multifaceted challenges, resulting in delays and misdiagnoses. A significant obstacle is the disease's diverse manifestations, which make small lesions difficult to detect without specialised diagnostic tools. Moreover, the nonspecific nature of endometriosis symptoms, such as pelvic pain, heavy menstrual bleeding, and dyspareunia, overlaps with those of other gynaecological and gastrointestinal conditions, further complicating the diagnostic journey. (Dantkale & Agrawal, 2024) The lack of reliable screening tools exacerbates the challenge, as conventional imaging techniques such as ultrasound and MRI may not be sufficient for effective endometriosis detection. Furthermore, the normalisation of menstrual pain and a general lack of awareness or education about female health contribute to symptom dismissal or underestimation, leading to delayed or missed diagnoses. This delay in diagnosis, averaging between 7 and 11 years, significantly impacts women's mental health, quality of life, and overall well-being. Additionally, inflammation surrounding abnormal endometrial tissue can complicate the biopsy process, potentially obscuring the microscopic structure necessary for an accurate diagnosis. The complexity of endometriosis symptoms, coupled with the absence of specific diagnostic tools and the normalisation of menstrual pain, poses substantial challenges in diagnosing the condition, often resulting in delays and misdiagnoses that profoundly affect women's health and quality of life.(Dantkale & Agrawal, 2024)

Socioeconomic and Cultural Barriers to Accessing Diagnosis: Socioeconomic and cultural barriers exert a significant influence on accessing timely diagnosis for endometriosis. Research underscores disparities in access to care, diagnosis, treatment, and management of endometriosis among various racial and socioeconomic groups in the United States. Studies reveal that non-White women encounter challenges in receiving appropriate care, with Black women experiencing elevated rates of perioperative complications, mortality, and prolonged perioperative stages compared to other racial and ethnic groups. These disparities underscore the imperative for further research to address diagnostic and treatment gaps beyond surgical management and socioeconomic hurdles. (Dantkale & Agrawal, 2024)Cultural factors also have a crucial impact on delayed diagnosis, as societal perceptions of womanhood and menstruation

may normalise symptoms, impeding healthcare providers' recognition of endometriosis. Furthermore, the stigma surrounding menstruation and the misconception that endometriosis primarily affects white,middle-class women contribute to diagnostic biases and inadequate care for individuals from diverse racial and ethnic backgrounds. These cultural beliefs, coupled with socioeconomic inequities, erect substantial barriers to accessing proper diagnosis and treatment for endometriosis, underscoring the necessity of addressing these issues to enhance healthcare equity and outcomes for all individuals affected by the condition(Dantkale & Agrawal, 2024).

2.2 Symptom overlap: endometriosis

Developing effective clinical guidelines for the management of dysmenorrhea, endometriosis, and chronic pelvic pain is complicated due to their overlapping symptomatology, a lack of biomarkers, and the requirement that women undergo laparoscopic surgery to determine whether endometriosis lesions are present.9 In addition, confounding factors, potentially including a past history of sexually distressing events, may modify the pain experience. (Evans et al., 2018)

While several studies have linked a laparoscopic diagnosis of endometriosis with a wide range of additional symptoms at a rate higher than the general population, 11–15, few papers have investigated the frequency of these symptoms in women presenting with dysmenorrhea in clinical practice. In addition, they have not determined whether a specific symptom profile is associated with the presence of endometriosis lesions. (Evans et al., 2018)

The lack of association between pain severity, presenting symptom profile and the presence of endometriotic lesions

Dysmenorrhea and pelvic pain have traditionally been associated with the presence of laparoscopically diagnosed endometriosis lesions. While these conditions commonly coexist, the relationship between the clinical symptoms with which a girl or woman presents to her health practitioner (dysmenorrhea) and the medical condition that may or may not be found at laparoscopy (endometriosis) remains controversial. A literature review by Janssen et al4 considered laparoscopic outcomes in adolescent girls aged 10–21 years presenting with pain. They found endometriosis lesions to be present in 62% of adolescents overall, in 75% of girls with chronic pelvic pain resistant to treatment with the oral contraceptive pill and anti-inflammatory medications, in 70% of girls with dysmenorrhea alone, and in 49% of girls with chronic pelvic pain not necessarily resistant to treatment. Additional factors affecting the experience of dysmenorrhea appear likely. A consensus paper published in 2013 included majority but not universal support for a statement describing a “philosophical shift to consideration of endometriosis and pelvic pain as a spectrum or continuum of disease”. It was recognised that this approach would avoid excluding women who lack laparoscopic confirmation of a diagnosis of endometriosis, yet have similar symptoms and associated diagnostic and therapeutic interventions. (Evans et al., 2018)

Endometriosis is a common comorbidity of pelvic pain syndrome (PPS)

Endometriosis and dysmenorrhea frequently coexist.4 However, the high frequency of symptoms in our study, both within and outside the pelvis, regardless of endometriosis status, supports the view that endometriosis and pain may be associated, rather than etiologically linked, conditions. They may share a similar underlying mechanism yet represent distinct clinical entities within a larger syndrome of associated symptoms and conditions. Both endometriosis and dysmenorrhea would then be common, but non-essential features of female PPS, much as polycystic ovaries are common, but non-essential, features of the systemic metabolic disorder, polycystic ovarian syndrome (PCOS). (Evans et al., 2018)

2.3 Overlap Between Irritable Bowel Syndrome Diagnosis and Endometriosis in Adolescents

More adolescents with endometriosis (54 of 224; 24%) had comorbid IBS compared with adolescents without endometriosis (7 of 99; 7.1%). The odds of IBS were 5.26-fold higher among participants with endometriosis than without (95% CI, 2.13–13.0). In girls with severe acyclic pelvic pain, the odds of IBS were 35.7-fold higher in girls without endometriosis (95% CI, 4.67–272.6) and 12-fold higher in girls with endometriosis (95% CI, 4.2–36.3), compared with no/mild pain. For participants with endometriosis, each 1-point increase in acyclic pain severity increased the odds of IBS by 31% (adjusted odds ratio, 1.31; 95% CI, 1.18–1.47).(DiVasta et al., 2021)

2.4 Shared Symptoms and Subfertility

"In the operative cohort, a history of subfertility was associated with a higher adjusted probability of having both conditions (adjusted prevalence ratio, 10.33; 95% confidence interval, 3.94−27.08), followed by having endometriosis only (adjusted prevalence ratio, 2.45; 95% confidence interval, 1.56−3.84) or polycystic ovarian syndrome only (adjusted prevalence ratio, 1.15; 95% confidence interval, 0.51−2.61), than having neither condition." (Schliep et al., 2023)

"In addition, experiencing chronic pelvic pain within the past 12 months was associated with a higher probability of having both conditions (adjusted prevalence ratio, 2.53; 95% confidence interval, 1.07−6.00) than having neither condition." (Schliep et al., 2023)

"Our findings showed that the co-occurrence of endometriosis and PCOS, within the operative cohort, was associated with a 10-fold higher probability of subfertility, followed by a 3-fold higher probability among women with endometriosis and a 1.2-fold higher probability among women with PCOS only, than having neither condition." (Schliep et al., 2023)

"Our study informs the clinical enigma of sustained subfertility among women with PCOS once ovulatory status has been restored; the coexistence of endometriosis may be a common contributing factor." (Schliep et al., 2023)

In addition, although chronic pelvic pain was higher in women with endometriosis and/or PCOS than in women with neither condition, painful menstrual cramps (dysmenorrhea) showed the strongest relationship with having both conditions. Previous research has reported that 74% of women with PCOS experiencing chronic or cyclic pelvic pain and/or subfertility also have endometriosis lesions. Although most women's health clinicians and researchers associate endometriosis with chronic pelvic pain and dysmenorrhea, women with PCOS are also at increased risk of dysmenorrhea(Schliep et al., 2023)

2.5 Analysis of psychopathological comorbidity behind the common symptoms and signs of endometriosis

Higher levels of somatisation, depression, sensitivity and anxiety were found in the Endometriosis Group compared with the Control Group.(Leone Roberti Maggiore et al., 2016)

The Endometriosis Group was formed by 166 patients (mean age: 36 ± 6 yrs) matched with 48 controls (mean age: 38.4 ± 12.8 yrs). Somatisation ($p = 0.02$), depression ($p = 0.01$), sensitivity ($p = 0.04$), and phobic anxiety ($p = 0.04$) were higher in the Endometriosis Group than in the Control Group. The Endometriosis Group was further characterised by significantly higher levels of anxiety than the Control Group ($p = 0.03$) as assessed by the Self-Rating Anxiety Scale. Regarding the Quality of Life Index, a significant health decline in the Endometriosis Group compared with the Control Group ($p = 0.008$) was found.Higher levels of somatisation, depression, sensitivity and anxiety were found in the Endometriosis Group compared with the Control Group. (Leone Roberti Maggiore et al., 2016)

a. Misdiagnosis of endometriosis

1. **Suspicion of malignant degeneration of decidualized endometriosis: imaging pattern and treatment issues**

   The sonographic pattern of decidualized ovarian endometriomas, in a proportion of cases, may mimic malignancy (Mascilini et al., 2014). As better described in depth later on, solid components can be easily recognised, and the echogenicity of the cyst content is usually ground-glass or low level. The content usually consists of papillary projections with a smooth, rounded contour. Colour Doppler analysis can detect multiple vascularisation signals within the solid part with a low resistance index.(Leone Roberti Maggiore et al., 2016)

2. **Decidualized ovarian endometriosis in pregnancy: diagnosis**

   Furthermore, as mentioned above, pregnancy-related hormonal status may effectively lead to changes in the histologic, sonographic and molecular appearance referred to as ‘decidualization’, which may in some cases resemble malignant ovarian tumours, potentially leading to an

unnecessary surgical intervention.(Leone Roberti Maggiore et al., 2016)

3. **Decidualized endometriosis in extra-ovarian sites**
   Given its rarity, such a condition might be misdiagnosed as a malignant disease (Bergqvist, 1993; Nogales et al., 1993). Peritoneal deciduosis in pregnancy mimicking carcinomatosis has been reported (Adhikari & Shen, 2013).(Leone Roberti Maggiore et al., 2016)

4. **Bowel**
   Nonspecific symptoms (acute abdominal pain, nausea and vomiting) were experienced in 94% of the patients (15/16). Notably, in two cases, pyelonephritis was suspected, delaying the diagnosis and in three cases, bowel perforation was not diagnosed during the first exploratory laparotomy, thus requiring a second laparotomy (Pisanu et al., 2010; Setu'bal et al., 2014**).(**Leone Roberti Maggiore et al., 2016)
   Acute appendicitis and endometriosis of the appendix show no differences in population features (age, parity, pregnancy duration at diagnosis) and presenting signs and symptoms; therefore, it is challenging to make a differential diagnosis before histological examination.(Leone Roberti Maggiore et al., 2016)

5. **Adnexa**
   In three cases of infected endometrioma (Phupong et al., 2004; Ueda et al., 2010, Dogan et al., 2012), symptoms and signs mimicking any cause of acute abdomen led to surgery during pregnancy with drainage of the abscess (Table VI). In one case, surgery was performed at 35 weeks of gestation for the clinical suspicion of acute appendicitis (Phupong et al., 2004); in the second case, drainage of the ovarian abscess was performed in the second trimester (Ueda et al., 2010). Dogan et al. (2012) reported the case of a 30-year-old woman who underwent firstly appendectomy at 24 weeks' gestation for acute appendicitis due to decidualized endometriosis.(Leone Roberti Maggiore et al., 2016)
   Primary care physicians, including general practitioners (GPs), often overlook endometriosis-related symptoms or misdiagnose them as other benign or unrelated illnesses. The diagnostic challenge associated with endometriosis stems from its diverse and non-specific manifestations and the fact that it may mimic other conditions such as irritable bowel syndrome (IBS) and pelvic inflammatory disease (PID)(Li et al., 2025). Provider-related factors were equally important, with many studies describing general practitioners' (GPs') misdiagnosis and dismissal of symptoms by non-specialists. Ballard et al. and Staal et al. noted that GPs tend to dismiss symptoms as IBS or stress-related pelvic pain, thereby not referring to specialists.(Li et al., 2025)Ballard et al. and Staal et al. showed that general practitioners and other non-specialists frequently either denied or explained away symptoms. Symptoms of IBS, chronic appendicitis, or some forms of psychological disorders were often misinterpreted, leading to either a too-long diagnostic process or unwarranted treatments and further suffering. (Li et al., 2025)

6. **Endometriosis diagnosis challenges: differential diagnosis, pelvic pain**
   Endometriosis is one of the most widespread gynaecological disorders and a very common condition amongst fertile women; thus, it has to be considered one of the possible sources of lumbopelvic pain. Endometriosis is commonly related to low back pain (LBP) and, therefore, often mistaken for a musculoskeletal disorder. (Cricco et al., 2021)
   Ultrasound is an effective tool to detect and characterise endometriosis lesions. Variances in endometriosis lesions' appearance and distorted anatomy secondary to adhesions and fibrosis present as major difficulties during the complete sonographic evaluation of pelvic endometriosis. Currently, the differential diagnosis of endometriosis to distinguish it from other diseases represents the hardest challenge and affects subsequent treatment. Several gynaecological and non-gynaecological conditions can mimic deep-infiltrating endometriosis. For example, abdominopelvic endometriosis may present as atypical lesions by ultrasound. Here, we present an overview of benign and malignant diseases that may resemble endometriosis of the internal

genitalia, bowels, bladder, ureter, peritoneum, retroperitoneum, as well as less common locations.(Scioscia & Laganà, 2020)

Invasive diagnosis (laparoscopy is the gold standard)

The diagnosis of endometriosis remains a challenge despite years of investigation and research in this area. While many clinicians continue to rely on surgical and histological confirmation to diagnose endometriosis, we highlight here that all methods of diagnosis are imperfect and subject to limitations. On the other hand, all methods have strengths. The strengths, limitations and reported sensitivities and specificities of diagnostic methods for endometriosis are summarised in Table 1(Pascoal et al., 2022)

Diagnostic Modality	Strengths	Limitations	Diagnostic Accuracy
Clinical History	Non-invasive; Feasible, low-cost; Symptomatology can predict disease location; May facilitate therapeutic alliance; May guide treatment choice, depending on complaints	Common symptoms of endometriosis have wide differential diagnosis; Symptoms not predictive of disease extent	Sn, 76–98%; Sp, 20–58%
Physical Examination	Accessible; High specificity; Opportunity to detect DE by visualization or palpation	Low sensitivity; Outcomes are operator-dependent; Diagnostic accuracy varies by disease location; Examination may be considered invasive and painful	Sn, 18–88%; Sp, 76–100%
Biomarkers	Objective measure; Combination may rule in endometriosis as a triage test (further research required)	Dependent on laboratory techniques and quality control protocols; Some vary with hormonal and menstrual fluctuations; Some are not specific to endometriosis; Cannot discern DE, OE or SE	Anti-endometrial antibodies: Sn, 81%; Sp, 75%; IL-6: Sn, 63%; Sp, 69%; CA 19-9: Sn, 36%; Sp, 87%; CA 125: varies by cut-off used
Ultrasound	High specificity and sensitivity for OE; Overall high accuracy in detecting DE and POD obliteration; Dynamic nature for organ mobility; Allows anatomic mapping; Opportunity to provide visual evidence to patients; High tolerability; Cost-effective	Limited ability to detect SE; Detection of DE requires highly trained sonographers/sonologists; Outcomes are operator-dependent; Examination may be considered invasive and painful	SE: Sn, 65–79%; Sp, 91–95%; OE: Sn, 93%; Sp, 96%; DE: Sn, 79%; Sp, 94%
MRI	Images obtained appear the same to all viewers;	Limited ability to detect SE; Variable imaging protocols	SE: Sn, 79%; Sp, 72%; OE:

Diagnostic Modality	Strengths	Limitations	Diagnostic Accuracy
	Overall high accuracy in detecting DE and extrapelvic endometriosis; Allows anatomic mapping; Opportunity to provide visual evidence to patients; Static assessment	reported in literature; Low accuracy in defining bowel depth of invasion; Requires specific training endometriosis; No consensus on how to describe findings; High cost compared with ultrasound	Sn, 95%; Sp, 91%; DE: Sn, 94%; Sp, 77%
Laparoscopy	Overall high accuracy, considered gold standard; Allows concomitant diagnosis and treatment; Opportunity to provide visual evidence to patients; Significant placebo effect	Invasive, carries surgical risk; Diagnostic accuracy dependent on surgical experience; Visual diagnosis challenged by heterogeneous lesion appearance, inaccessible lesions	Sn, 90–94%; Sp, 40–79%
Histology	Ultimate confirmation of diagnosis; Can rule out other conditions; Can diagnose without visual confirmation	Obtaining tissue for histology requires surgical excision; Influenced by surgical environment and method of resection	Not available

. Although non-invasive diagnostic methods, such as clinical assessment, biomarkers and imaging, have not yet qualified as replacement tests for surgery in diagnosing all types of endometrioses in the DTA literature, these methods may be sufficient in many clinical scenarios to provide people with a 'rule-in' diagnosis. **(Pascoal et al., 2022)** Preoperative TVUS-BP was accurate for the identification of all sites of ovarian and deep endometriosis that were evaluated. It had a significantly higher sensitivity than DL to detect rectosigmoid endometriosis, and it was able to correctly predict intraoperative ASRM staging as well as the Enzian score. These results suggest that TVUSBP can replace DL for the diagnostic and treatment planning of patients with ovarian and deep endometriosis. Screening patients in this way requires advanced diagnostic centres with gynaecologists who are experienced in endometriosis to obtain the best results for the patient. (Goncalves et al., 2021)

2.7 Minimally invasive diagnostics" endometriosis

laparoscopy, exposing patients to potentially serious complications, and is often delayed. Non-invasive biomarkers are urgently required to accelerate diagnosis and for triaging potential patients for surgery. **(Irungu et al., 2019)**Different research groups have investigated the role of miRNAs (microRNAs or miR) in the regulation of known genes, given their association with processes involved in disease pathogenesis and progression. (Monnaka et al., 2021) miRNAs are a class of small endogenous, non-coding RNA molecules involved in post-transcriptional regulation of gene expression. (Marí-Alexandre et al., 2016) These small molecules have also been found in peripheral blood and may therefore be potential diagnostic biomarkers for endometriosis.(Lin & Yang, 2011)(Wang et al., 2013(Monnaka et al., 2021)

No particular miRNA or miRNA combination has been validated for improved diagnosis of endometriosis to date. This may have reflected the heterogeneity of the disease and resultant differences in tissue composition. Large databases comprising data derived from samples collected from patients with well-characterised endometriosis may play a key role in biomarker investigation in future studies.

The use of saliva and vaginal fluid samples for miRNA identification could be a potential non-invasive solution to overcome current barriers to the diagnosis of endometriosis. (Monnaka et al., 2021) Tissue heterogeneity and blood contamination is likely to have hindered biomarker discovery, whilst a small sample size precludes accurate determination of performance by cycle phase. Independent validation of these biomarker panels in a larger cohort is however warranted, and if successful, they may have clinical utility in triaging patients for surgery. (Monnaka et al., 2021) Cycle phase and endometriosis-associated proteomic changes were identified in eutopic tissue from over 1400 identified gene products, yielding potential biomarker candidates. Bioinformatics analysis revealed enrichment of adhesion/extracellular matrix proteins and progesterone signalling. The best single marker for discriminating endometriosis from controls remained CA125 (AUC = 0.63), with the best cross-validated multimarker models improving the AUC to 0.71–0.81, depending upon menstrual cycle phase and control group. . (Monnaka et al., 2021)Molecular changes associated with endometriosis in eutopic and ectopic tissue and have derived non-invasive, cycle phase-specific diagnostic models for endometriosis with respectable performance characteristics that are similar, if not better, than those reported previously.(Monnaka et al., 2021)

None of the imaging methods was accurate enough to provide this information on overall pelvic endometriosis. Transvaginal ultrasound identified ovarian endometriosis with enough accuracy to help surgeons determine whether surgery was needed, and magnetic resonance imaging (MRI) was sufficiently accurate to replace surgery in diagnosing endometrioma but was evaluated in only a small number of studies. Other imaging tests were assessed in small individual studies and could not be evaluated in a meaningful way. Transvaginal ultrasound could be used to locate more anatomical sites of deep endometriosis when compared with MRI, helping surgeons better plan an operative procedure. Endometriosis in the lower bowel appears to be relatively accurately identified by both transvaginal and transrectal ultrasound, by MRI and by multi-detector computerised tomography enema. New types of ultrasound and MRI show a lot of promise in detecting endometriosis but studies are too few to clearly show their diagnostic value.(Nisenblat et al., 2016)

2.8 Diagnostic accuracy of laparoscopy "endometriosis

According to ASRM, approximately 50% of patients with unexplained infertility may have undiagnosed endometriosis (8). Although women diagnosed with unexplained infertility and recurrent pregnancy loss undergo IVF treatments, they seldom seek surgical diagnosis of endometriosis, even though persistent endometriosis could affect the success rate of IVF(Nezhat et al., 2022). Testing for endometrial BCL-6 may help determine high-risk endometriosis patients with other inflammatory pathologies who could be good surgical candidates. Endometrial BCL-6 testing has a high PPV that could help physicians and patients undergoing infertility treatment to seek surgical evaluation for endometriosis, to improve their reproductive outcomes(Nezhat et al., 2022)

Surgical diagnosis consisting of laparoscopy, with or without histologic confirmation, is still considered the gold standard for the diagnosis of endometriosis. (Nezhat et al., 2022)

Endometrial BCL-6 testing has a high positive predictive value that could help physicians and patients undergoing infertility treatment to seek surgical evaluation for endometriosis, to improve their reproductive outcomes. (J Turk Ger Gynecol Assoc 2022; 23: 117-9)

2.9 Biomarkers for the Noninvasive Diagnosis of Endometriosis

A biomarker or a panel of biomarkers is easy to measure, usually noninvasive, and could benefit the clinician in both diagnosing and monitoring the treatment response. (Anastasiu et al., 2020)A noninvasive biomolecule for endometriosis diagnosis could be extracted and quantified from serum, plasma, or urine and would be beneficial for patients with chronic pelvic pain, infertility, and dysmenorrhea, in the context of a regular ultrasound.(Anastasiu et al., 2020)

Promising potential endometriosis biomarkers that underwent testing were: glycoproteins, growth factors, miRNAs, lncRNAs, as well as proteins related to the angiogenesis process or immunology(May et al.,

2010). No single miRNA or lncRNA was considered as a sole noninvasive biomarker(Anastasiu et al., 2020). Despite extensive research, neither a single biomarker nor a panel of biomolecules has been considered sufficiently specific and sensitive to be used as a diagnostic test for endometriosis.(May et al., 2010).

Of particular relevance is the significance of the fact that the initial presence of the ectopic foci can influence the gene expression pattern of the eutopic endometrium with disease progression (Gashaw, 2006). This shows that endometriosis is indeed a chronic inflammatory disease wherein the sterile inflammation induced by the cyclic deposition of menstrual fragments can lead to pathogenic epigenetic changes in the eutopic endometrium. (Ahn et al., 2017)

It is more likely that instead of a single biomarker, a group of biomarkers will provide improved diagnostic performance and minimise false positives and negatives during differential diagnosis. With the advent of the field of GWAS and improved understanding of the functional significance of SNPs and genetic variants associated with endometriosis risk, it may be feasible to identify a panel of diagnostic biomarkers composed of endometrial methylome and expression patterns of circulating noncoding RNA (i.e., miRNA and lncRNA), or even from endometrial biopsies, with reasonable specificity and sensitivity. (Ahn et al., 2017)

Strategies for non-invasive biomarker discovery

Studies seeking to uncover non-invasive biomarkers forendometriosis have employed two main experimental strategies:a hypothesis-driven approach or a high-throughputscreening “omics” approach. Thehypothesis-driven approach uses current knowledge ofendometriosis pathogenesis derived from animal models, in vitro experimental data, and in vivo data from patients topropose potential biomarkers for the disease that can thenbe tested in experimental and clinical studies. (Hudson et al., 2020)The potentialbiomarker, or combination of biomarkers, is then usually tested experimentally by comparing a cohort of patients and controls using small-scale multiplex experimental techniques like ELISA and reverse transcription quantitative PCR (RT-qPCR). In contrast, the “omics” screeningapproach uses high-throughput technologies such asRNA-seq, proteomics, and lipidomics to compare cohortsof control and endometriosis patients to identify candidatebiomarkers in an unbiased fashion.Despite numerous studies that have taken a diverse arrayof experimental approaches to uncover multiple candidate Non-invasive biomarkers for endometriosis, noclinically accepted biomarker is available(Hudson et al., 2020)

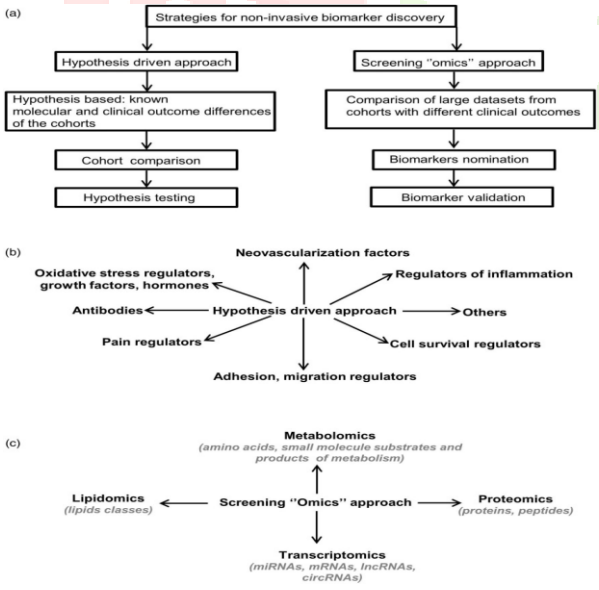

Fig no 1(Hudson et al., 2020)

Although non-invasive diagnostic methods, such as clinical assessment, biomarkers and imaging, have not yet qualified as replacement tests for surgery in diagnosing all types of endometriosis in the DTA literature, these methods may be sufficient in many clinical scenarios to provide people with a ‘rule-in’ diagnosis.(Pascoal et al., 2022)

Diagnostic Modality	Strengths	Limitations	Diagnostic Accuracy
Clinical History	Non-invasive Feasible, low-cost Symptomatology can predict disease location May facilitate therapeutic alliance May guide treatment choice, depending on complaints	Common symptoms of endometriosis have wide differential diagnosis Symptoms not predictive of disease extent	Sn, 76–98%; Sp, 20–58% (Pascoal et al., 2022)
Physical Examination	Accessible High specificity Opportunity to detect DE by visualization or palpation	Low sensitivity Outcomes are operator-dependent Diagnostic accuracy varies by disease location Examination may be considered invasive and painful	Sn, 18–88%; Sp, 76–100% (Pascoal et al., 2022)
Biomarkers	Objective measure Combination may rule in endometriosis as a triage test (further research required)	l Dependent on laboratory techniques and quality control protocols Some vary with hormonal and menstrual fluctuations Some are not specific to endometriosis Cannot discern DE, OE or SE	Anti-endometrial antibodies: Sn, 81%; Sp, 75%133 IL-6: Sn, 63%; Sp, 69%132 CA 19-9: Sn, 36%; Sp, 87%132 CA 125: varies by cut-off used132 (Pascoal et al., 2022)
Ultrasound	High specificity and sensitivity for OE Overall high accuracy in detecting DE and POD obliteration Dynamic nature for organ mobility Allows anatomic mapping Opportunity to provide visual evidence to patients High tolerability Cost-effective	Limited ability to detect SE Detection of DE requires highly trained sonographers/sonologists Outcomes are operator-dependent Examination may be considered invasive and painful	SE: Sn, 65–79%; Sp, 91–95%71 OE: Sn, 93%; Sp, 96%71 DE: Sn, 79%; Sp, 94%71 **(Pascoal et al., 2022)**
MRI	images obtained appear	Static assessment	SE: Sn, 79%; Sp,

	the same to all viewers Overall high accuracy in detecting DE and extrapelvic endometriosis Allows anatomic mapping Opportunity to provide visual evidence to patients	Limited ability to detect SE Variable imaging protocols reported in literature Low accuracy in defining bowel depth of invasion Requires specific training endometriosis No consensus on how to describe findings High cost compared with ultrasound	72%71 OE: Sn, 95%; Sp, 91%71 DE: Sn, 94%; Sp, 77%71 (Pascoal et al., 2022)
Laparoscopy	Overall high accuracy, considered gold standard Allows concomitant diagnosis and treatment Opportunity to provide visual evidence to patients Significant placebo effect	Invasive, carries surgical risk Diagnostic accuracy dependent on surgical experience Visual diagnosis challenged by heterogeneous lesion appearance, inaccessible lesions	Sn, 90–94%; Sp, 40–79%
Histology	Ultimate confirmation of diagnosis Can rule out other conditions Can diagnose without visual confirmation	Obtaining tissue for histology requires surgical excision Influenced by surgical environment and method of resection	Not available (Pascoal et al., 2022)

2.10 Novel therapeutics" for endometriosis

Endometriosis is a heterogeneous disease with a complex pathogenesis. Thus, a single-molecular model is insufficient to explain endometriosis-related infertility(Vanhie et al., 2016). Endometriosis is a very complex disease, and the exact pathophysiology and pathogenesis have not yet been elucidated. Over the last two decades major advances in the understanding of the pathophysiology have been made, showing an important role for angiogenesis, inflammation and alterations in the endometrium and immune system. These insights have opened new strategies for the development of novel therapies for endometriosis focusing on immune-modulating, anti-angiogenic and anti-inflammatory agents. Unfortunately, none of these promising novel agents have passed the stages of pre-clinical research so far. The difficulties in translation of new therapeutic strategies from pre-clinical research to clinical trials and daily clinical practice can partially be attributed to the complexity of the disease but also to shortcomings in the in vitro and in vivo models used, problems in design of pre-clinical trials and in the patient selection of clinical trials. (Ramin-Pachero et al., 2015)

2.11 Novel therapeutics for endometriosis

Endometriosis is a common benign disease that mainly affects women of childbearing age. Despite being a common condition, itspathogenesis remains unclear. Many women will experience the phenomenon such as retrograde menstruation after menarche, but the incidence rate of endometriosis is low, which indicates that not all endometrial tissues can invade the pelvic and abdominal cavities. (Li et al., 2023)Moreover, it has been seen that the abnormal immune response mediated by immune cells causes ectopic growth of endometrial cells. Traditionally, medical treatment of endometriosis primarily includes surgery and hormone therapy. However, these methods are not satisfactory to date. The recurrence rate of this disease is high. Accumulating evidence suggests that several immunologic factors are probably

involved in the pathogenesis of endometriosis. These factors directly or indirectly promote the development of endometriosis. These findings have provided novel insights into the treatment strategy of endometriosis. An increasing number of studies have suggested that the medical methods targeting these immunologic factors inhibit the development of endometriosis across different aspects This is probably a milestone in the treatment of this disease. However, information on the clinical application of immunotherapy in endometriosis is very limited and detailed mechanisms need to be further investigated.(Li et al., 2023)

Mechanism of action(Li et al., 2023)

1. Anti-TGF-β preparation
2. The nuclear factor kappaB-targeted inhibitor
3. Complement system inhibitors

Preclinical evidence(Li et al., 2023)

1. Immunotherapy based on the CD47SIRPa signaling pathway
2. Anti-exocrine therapy
3. Oral Lactobacillus gasseri OLL2809
4. An extract of the white mistletoe tree Helixor A
5. Targeted inhibition of PD-1
6. Loratadine
7. Anti-TNF preparation
8. Interleukin preparation
9. Recombinant INF-2b
10. COX-2 inhibitor
11. Statins
12. Mesenchymal stem cells
13. Vitamin D
14. Bacillus Calmette–Guérin

2.12 Data fragmentation across hospitals, imaging centres, and research institutes

Endometriosis biomarker discovery is that the small-scale nature and variability in the design of most studies have made the independent validation of biomarker candidates difficult. To address this, efforts are underway to standardise patient cohorts, data, and sample collection to allow for better cross-study comparisons. Given the complexity and heterogeneity of the disease, large-scale multi-centre studies using this standardised approach are necessary to both validate existing biomarker candidates and uncover potential new markers. (Hudson et al., 2020)

A key challenge in multi-centre studies is the heterogeneity of patient cohorts resulting from different recruitment methods. As this study demonstrates, women with endometriosis recruited through self-help groups reported psychosomatic diseases and symptoms, as well as endometriosis-related pain and fatigue, significantly more frequently than those recruited in clinical settings ($p < 0.001$). This finding highlights the need for careful consideration of recruitment channels to ensure the comparability and generalizability of data across different study sites. (Candan et al., 2025)

A valuable resource for endometriosis research is large-scale population-based databases. In one study, the computerised databases of Maccabi Healthcare Services (MHS), which represent a quarter of the Israeli population, were used to conduct a retrospective population-based study. (Eisenberg et al., 2018)This database allowed for the assessment of crude point prevalence and annual incidence rates of diagnosed endometriosis (ICD-9-CM 617.xx). The researchers were also able to characterise patients based on sociodemographic and clinical characteristics, including data from validated infertility and chronic disease registries.(Eisenberg et al., 2018)

The study used the **Endeavour tool** to **integrate 6 data sources**: gene ontology, protein domains from InterPro, KEGG pathway, microarray expression, gene network from STRING, and transcriptional motifs from TRANSFAC. This process generated a highly reliable set of endometriosis-related genes. **P53** is a tumor suppressor gene crucial for regulating cell growth and preventing cancer (Kern et al., 1991). Studies have linked aneuploidy of chromosome 17 to endometriosis, and a significant decrease in TP53

protein has been observed in ovarian lesions (Kosugi et al., 1999; Allavena et al., 2015). Furthermore, a common genetic variation (SNP) in this gene is associated with increased susceptibility to the disease (Ammendola et al., 2008; Camargo-Kosugi et al., 2014; Chang et al., 2002; Gallegos-Arreola et al., 2012; Hsieh & Lin, 2006; Lattuada et al., 2004; Ying et al., 2011)(Liu & Zhao, 2016).**VEGFA** is a critical **angiogenic factor**, essential for the formation of new blood vessels that allow ectopic endometrial tissue to survive (Groothuis et al., 2005). Elevated levels of VEGFA have been found in the peritoneal fluid and serum of women with endometriosis (Kupker et al., 1998; McLaren et al., 1996; Oliveira et al., 2005).
AKT1, a protein kinase, is highly activated in the endometrial stromal cells of women with endometriosis (Laudanski et al., 2014; Laudanski et al., 2009). Overactive AKT1 not only promotes cell proliferation and survival but also interferes with normal decidualization (Yin et al., 2012; Kim et al., 2014).
MMP9, a zinc metalloprotease, degrades the extracellular matrix (Nagase et al., 1992). Higher expression of MMP9 mRNA is associated with clinically aggressive lesions, suggesting its role in the survival and invasion of endometriotic tissue (Ueda et al., 2002).
This gene set was further used as a "seed" to predict novel candidate genes, providing in-depth insights into the molecular mechanisms of endometriosis pathogenesis.(Liu & Zhao, 2016)
In contrast to traditional biorepositories, the consolidation of heterogeneous datasets and biospecimens from various distributed systems, clinical studies, and research institutions, into a data commons presents important opportunities to drive translational medicine.(Asiimwe et al., 2021)The establishment of an **integrated data commons** at OVCARE successfully transformed a collection of **data silos** into a unified infrastructure. This approach directly addresses the challenge of fragmented data, helping to **break barriers to the access of large datasets** needed to study complex and rare diseases.(Asiimwe et al., 2021)

The amount of data in our medical systems has steadily increased with the advent of electronic medical records and increased computing power. (Rath et al., 2022)As a result, in the healthcare industry, implementing a solid data analytics platform has become critical. The process of generating actionable insights by defining problems and applying statistical models and analysis to existing data is referred to as data analytics. The analysis of this large dataset can be used to generate data that will help doctors diagnose diseases earlier and more accurately. Electronic Health Records (EHR) have been incorporated to provide more coordinated and patient-centred care. (Rath et al., 2022)The use of Electronic Health Records (EHRs) in the ICU significantly reduces central line-associated bloodstream infections and surgical intensive care unit mortality rates. Electronic Health Records (EHR) provide secure access to patient data, which improves care quality and productivity. Electronic Health Records (EHR) systems have been used to manage chronic diseases such as diabetes, and it has been discovered that if providers participate in health information exchanges, regular use of the Electronic Health Records (EHR) can reduce data fragmentation and increase provider continuity of care. Using patient data, specialized AI systems assist specialists in their clinical workflow by recognizing and diagnosing various diseases. In the emergency department (ED), using a decision tree with Electronic Health Records (EHR) improves medical decision making, increases patient quality of life, and is cost-effective. Another cost-benefit analysis of using Electronic Health Records (EHR) to collect data yielded encouraging results. Regular use of Electronic Health Records (EHR) can reduce data fragmentation and increase provider continuity of care, especially when providers participate in health information exchanges.**(Rath et al., 2022).**
So far, EHRs have largely consisted of unstructured, narrative text and, to a small extent, of structured coded data. In the future, it will be necessary to implement more systematic terminologies and codes so that the data contained in EHRs can be put to better use(Wood et al., 2014). Two widely used clinical healthcare terminology databases are the ICD (International Classification of Diseases) and SNOMED-CT (Systematised Nomenclature of Medicine Clinical Terms), developed and supported by the WHO (World Health Organisation) and IHTSDO (International Health Terminology Standards Development Organisation), respectively (World Health Organization [WHO], n.d.)(International Health Terminology Standards Development Organization [IHTSDO], n.d.). Using standardised nomenclature in EHRs is important from a research perspective: the development of strategies for automatic or convenient use of this nomenclature is essential for the integration of routine clinical practice and scientific research. Furthermore, the consistent use of standardised nomenclature not only facilitates data extraction from

EHRs but also creates the possibility to exchange, integrate, and compare data from different EHRs. This "semantic interoperability" is on top of the Health Informatics agenda. It targets the preservation of meaning between heterogeneous patient-related and aggregated population data across different vocabularies and coding systems. In order to meet this demand, the WHO and IHTSDO have decided to create a Common Ontology(Rodrigues et al., 2014).

3. AI/ML Approaches for Early Diagnosis

3.1 Symptom-Based Prediction Models

To address the significant diagnostic delay of 6 to 10 years for endometriosis, a novel approach using machine learning has been developed to create a non-invasive, symptom-based screening tool. (Goldstein & Cohen, 2023) Unlike previous studies that relied on data from women already undergoing diagnostic procedures, this model is designed for use at the early stages of symptom onset. The best-performing model, an AdaBoost classifier, was trained on a set of patient questionnaires and achieved an impressive AUC of 0.94, with a sensitivity of 0.93 and a specificity of 0.95. This model relies on an optimised subset of just 24 symptoms and is intended to be incorporated into a website, allowing women to self-test and be referred for further examination at an earlier stage, thereby significantly shortening the time to diagnosis. (Goldstein & Cohen, 2023)

For the predictive modelling, four types of classification algorithms were trained: **Decision Tree, Random Forest, Gradient Boosting Trees, and Adaptive Boosting (AdaBoost)**. The **AdaBoost model** proved to be the most effective, achieving a high-performance profile with an **AUC of 0.94**, **sensitivity of 0.93**, **specificity of 0.95**, and **F1-score of 0.94**. (Goldstein & Cohen, 2023)

Supervised learning models (SVM, RF, XGBoost) for symptom clusters

Enhancing the diagnostic efficiency of endometriosis, researchers utilised multiple supervised machine learning techniques, including **Support Vector Machine**, **Random Forest**, and **XGBoost**, to construct predictive models. This novel diagnostic approach integrated a variety of genetic biomarkers rather than traditional single biomarkers. The study trained models on differentially expressed genes (DEGs) and identified a panel of five key diagnostic genes (**FOS, EPHX1, DLGAP5, PCSK5, and ADAT1**) using the LASSO algorithm. (Zhang et al., 2023)This gene combination demonstrated superior predictive performance, with an **AUC of 0.836**, and was validated in external datasets. The findings suggest that a combination of these genes can serve as a diagnostic tool and provide new insights into the pathogenesis of endometriosis by showing a close relationship with immune-infiltrating cells. (Zhang et al., 2023)

Model training
Generality

Machine Learning, Deep Learning, and ensemble models are trained to developp a diagnostic tool for endometriosis. ML models such as Logistic Regression (LR), Random Forest (RF), Decision Tree (DT), eXtreme Gradient Boosting (XGB), and hard/soft Voting Classifier are considered ensemble learning techniques28,29,30,31,32,33,34. A flowchart of the training protocols employed in this study is detailed in Fig. 2. (Bendifallah et al., 2022)

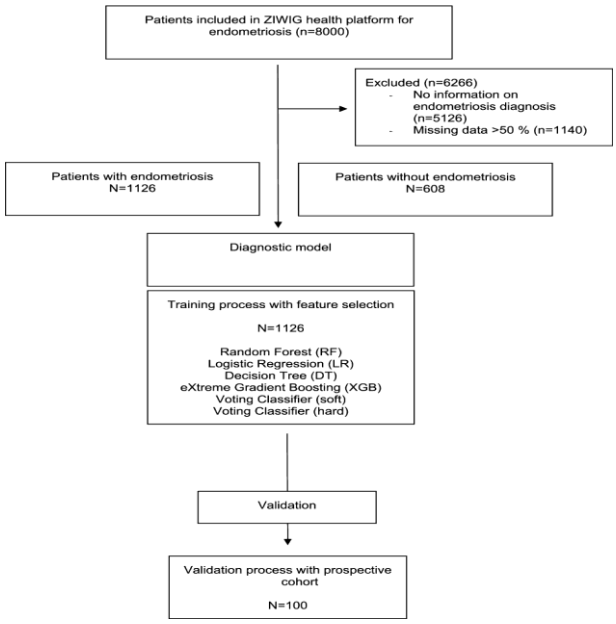

Fig 2: Model overview

Logistic Regression (LR) is a statistical model that uses a logistic function to model a binary dependent variable. Mathematically, a binary logistic model has a dependent variable with two possible values, where the two values are labeled "0" and "1". Outputs with more than two values are modeled by multinomial logistic regression. Logistic Regression is used in various fields, including healthcare and social sciences(Dreiseitl & Ohno-Machado, 2002).

Decision Tree (DT) is a simple and powerful machine learning model that utilizes any information obtained to find the best classification index of data samples. These classification indexes are the nodes of the DT, which then grow to form the tree structure. The DT model has already been successfully applied to research on public health and health behavior(Nguyen et al., 2021).

Random Forest (RF) classifier is an ensemble method that trains several DTs in parallel with bootstrapping followed by aggregation, jointly referred as bagging. Bootstrapping indicates that several individual DTs are trained in parallel on various subsets of a training dataset using different subsets of available features. Bootstrapping ensures that each individual DT in the RF is unique, which reduces the overall variance of the RF classifier. For the final decision, RF classifier aggregates the decisions of individual DTs and consequently exhibits good generalization (Nguyen et al., 2021)..

eXtreme Gradient Boosting (XGB) is a gradient boosting algorithm which is an ensemble of weak prediction models, mostly DTs. An individual tree is a simple, often unreliable, model but when multiple trees are grouped together, they can create a robust algorithm. XGB starts by creating a simple tree, which than progresses sequentially and builds upon the weaker learners, with each iteration revising the previous tree until an optimal point is reached, such as the number of trees (estimators) to build the solution(Geoffron et al., 2021).

Voting Classifier algorithm is a machine learning model that trains on an ensemble of numerous models and predicts an output (class) based on their highest probability of a chosen class as the output. It simply aggregates the findings of each classifier passed into Voting Classifier and predicts the output class based on the highest majority of voting. Voting classifier supports two types of voting: hard voting where the predicted output class is a class with the highest majority of votes; soft voting where the output class is the prediction based on the average of probability given to that class(Rocher et al., 2021).

Chi-Square Test: the Chi-square test is one of the most widely used non-parametric tests, often utilized to test the independence between observed and expected frequencies of one or more attributes in a contingency table. In this work, the Chi-square test was used to identify top significant features given the

dependent variable (Y)(Jouen et al., 2021).

Two datasets validate a diagnostic model for endometriosis: a training set of 1126 patients from the Ziwig Health platform and a separate validation set of 100 patients from the prospective ENDOmiARN study (NCT04728152).

The validation group consisted of 18- to 43-year-old women who had undergone a diagnostic or therapeutic laparoscopy. The study aimed to predict an endometriosis diagnosis, with the model's accuracy assessed using sensitivity, specificity, F1-score, and discrimination criteria.(Harrell et al., 1996)(Steyerberg et al., 2000)

The two datasets, training and validation, showed significant differences in their general and clinical characteristics, including patient demographics, symptom history, and medical treatments. (Bendifallah et al., 2022)

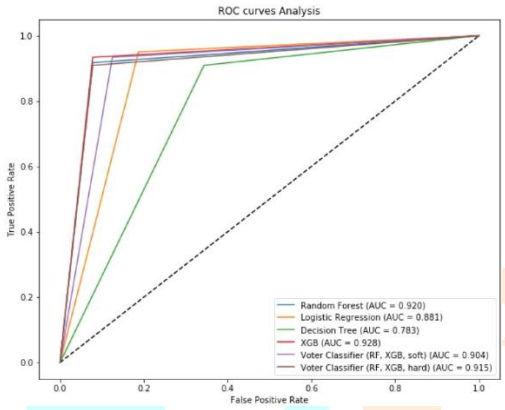

Fig 3

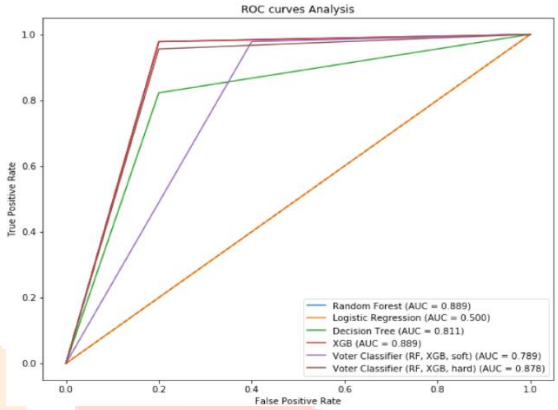

Fig 4

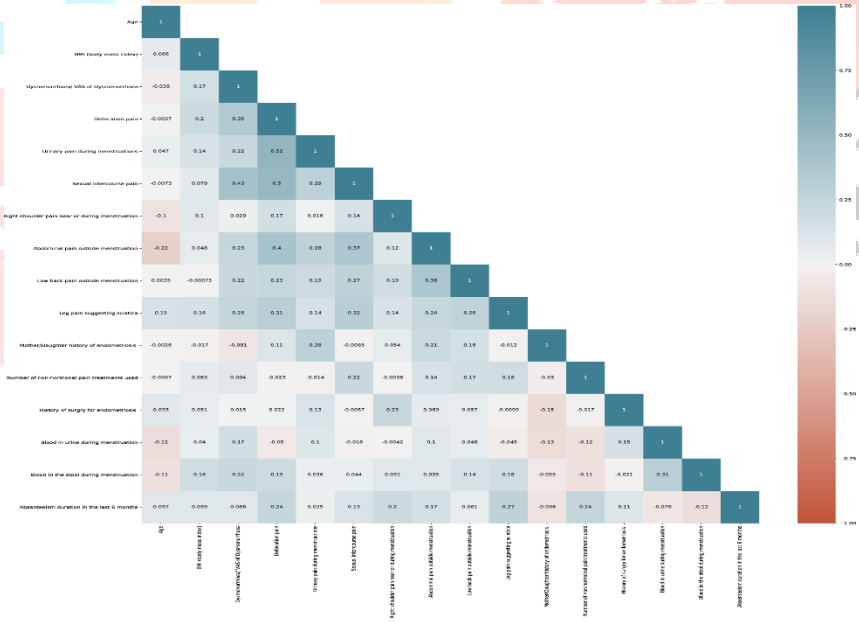

Fig 5

[Figure 1: ROC Curves for Machine Learning Classifiers on the Discovery Cohort; Figure 2: ROC Curves for Machine Learning Classifiers on the External Validation Cohort; Figure 3: Feature Correlation Matrix and Pathological Symptom Overlap Profiles (All data adapted from Bendifallah et al., 2022)]

- Use of digital health app data (e.g., Clue, Flo) and wearable inputs
- Digital health technologies are revolutionising endometriosis care through comprehensive symptom tracking and objective monitoring. Platforms like Flo, Clue, and Natural Cycles use AI for accurate forecasts and symptom analysis, with Clue's My Health Record feature using de-identified data to help close the diagnosis gap for female health conditions, including

endometriosis (European Commission, 2024). These applications enable real-time tracking of pain patterns, menstrual irregularities, and treatment responses, providing valuable data for clinical decision-making.

- Wearable sensors represent a paradigm shift toward objective pain assessment. Digital technologies, ranging from smartphone apps to wearable sensors, have shown potential toward facilitating chronic pain assessment and management (Parazzini et al., 2023). Symptom tracking through wearable devices may be particularly useful in endometriosis to minimise the burden of self-reporting and bias introduced by missing data (Parazzini et al., 2023). The SENSOPAD initiative addresses longstanding challenges by developing portable auxiliary devices for early endometriosis detection (European Commission, 2024).
- Recent systematic reviews identified 6 "good-quality" endometriosis mHealth apps that can be recommended to the endometriosis community (Zhang et al., 2025). However, many digital tools have not been specifically deployed or evaluated in patients with endometriosis-associated pain (Parazzini et al., 2023), highlighting the need for targeted validation studies. The integration of AI-powered analytics with continuous physiological monitoring through wearables promises personalised treatment optimisation and improved quality of life for endometriosis patients.

A baseline and a longitudinal questionnaire in the **Lucy app** collect real-world, self-reported information on symptoms of endometriosis, socio-demographics, mental and physical health, economic factors, nutritional, and other lifestyle factors. (Balogh et al., 2024)5,000 women with confirmed endometriosis and 5,000 women without diagnosed endometriosis in a control group will be enrolled and followed up for one year. With this information, any connections between recorded symptoms and endometriosis will be analysed using machine learning. (Balogh et al., 2024)

- **AI for Predicting High-Risk Endometriosis Profiles: Case Studies from Survey and EHR Data**

Artificial intelligence applications in endometriosis risk prediction have demonstrated remarkable clinical potential through comprehensive analysis of survey and electronic health record (EHR) data. A landmark UK Biobank study analyzed over 1,000 variables covering personal health information, lifestyle factors, self-reported data, genetic variants, and medical history to develop machine learning-based endometriosis prediction models (Chen et al., 2022). This comprehensive approach exemplifies how AI can synthesize multidimensional healthcare data for risk stratification.

Recent case studies showcase exceptional predictive performance. A 2024 study developed a self-report symptom-based prediction model achieving an area under the curve (AUC) of 0.94, with 93% sensitivity and 95% specificity (Nasir et al., 2024). The model was designed for web-based implementation as a self-diagnostic tool to reduce diagnostic delays by identifying high-risk individuals requiring further evaluation.

The latest 2025 research proposes supervised machine learning models for early endometriosis identification, emphasizing support for clinical decision-making given the disease's diverse etiology and symptom variability (Ruiz-Romo et al., 2025). Systematic reviews demonstrate that AI-based endometriosis applications consistently achieve pooled sensitivities ranging from 81.7% to 96.7% and specificities between 70.7% and 91.6% (Doherty et al., 2022).

3.2 Natural Language Processing (NLP) on Electronic Health Records

- **Extraction of phenotype data, symptom patterns, and misdiagnosis patterns**

A study found that patients with C1-INH-HAE commonly receive misdiagnoses, frequently allergic angioedema or appendicitis. The rarity of C1-INH-HAE, heterogeneity of its affected population, and the overlap in symptoms with other more common diseases make diagnosing C1-INH-HAE challenging. (Zanichelli et al., 2016)The present analysis is the first using IOS data to show that an initial misdiagnosis is a major driver of the long delays that patients can experience before a correct diagnosis is made. An initial misdiagnosis can have practical consequences for patients that can range from increased risk of death from laryngeal oedema to prolonged issues associated with an otherwise manageable condition. (Zanichelli et al., 2016)Considering that published data regarding C1-INH-HAE misdiagnosis are scarce and consist largely of case

reports, the relatively large real-world multinational database used in this analysis substantially contributes to the understanding of this issue. (Zanichelli et al., 2016)

Unsupervised machine learning has been effectively used to identify clinically meaningful endometriosis subtypes, or phenotypes, from patient-tracked data. These models can characterise a severe phenotype, uniquely associated with a high surgical burden and specific genitourinary symptoms, while also identifying other distinct subtypes characterised by hormonal treatment associations or regular menstruation.(Urteaga et al., 2020) Similarly, supervised learning models, such as an AdaBoost classifier, have been developed to identify specific symptom patterns, achieving high diagnostic accuracy with an AUC of 0.94 based on just 24 symptoms. This approach offers a powerful self-diagnostic tool to shorten the significant diagnostic delay caused by current methods. The challenge of diagnostic delay is further highlighted by studies on other complex conditions, which have shown that misdiagnosis is a major driver of this delay. (Urteaga et al., 2020)(Urteaga et al., 2020)

Data-driven characterisation of symptom clusters in chronic conditions is essential for shared cluster detection and physiological mechanism discovery. This study aims to computationally describe symptom documentation from electronic nursing notes and compare symptom clusters among patients with chronic conditions. (Koleck et al., 2021) We used a natural language processing application to identify the presence of symptoms. We calculated symptom documentation prevalence by note and patient, and conducted multiple correspondence analyses and hierarchical clustering to discover underlying groups of patients who have similar symptom profiles. As expected, pain was the most frequently documented symptom. (Koleck et al., 2021) All conditions had a group of patients characterised by no symptoms. In summary, we report both shared and distinct, as well as established and novel, symptom clusters across chronic conditions. Findings support the use of electronic health record-derived notes and natural language processing methods to study symptoms and symptom clusters to advance symptom science. (Koleck et al., 2021)

- **Temporal modeling of patient history using LSTMs and transformer-based NLP**

The use of transformer models to enhance NLP in MR administration is investigated. Renowned for their ability to understand contextual links along with efficiently handling large datasets, transformer designs provide clear improvements in the processing and analysis of medical language. Work improves the extraction, classification, and summarisation of data from complex medical records by use of models like BERT, GPT, and variants (Vasani et al., 2024). The study looks at how well these models may simplify data retrieval, increase the accuracy and relevance of CR, and support decision-making in medical environments. The results imply that the use of transformer-based NLP techniques might greatly boost the medical record administration, thereby improving patient care, accelerating procedures, and optimising data usage. Transformer models such as BERT are used in the research approach aiming at enhancing NLP in medical record handling. Literature, preprocessing EHRs, fine-tuning and assessment, along with pilot testing, all play a part. Maintaining ethical issues, a user interface is given for interaction. This method improves medical data handling effectiveness. BERT has shown promise in handling medical records in terms of enhancing identification and categorisation of medical entities found in data (Vasani et al., 2024). Various medical entities, including diseases, medications, procedures, and symptoms, have been specifically tailored into the strong language paradigm (Vasani et al., 2024). Confusion matrix performance measures reveal how well the model controls medical records. Future studies could investigate combining BERT with other advanced NLP methods, extending the dataset to include a wider range of medical records, using TLT in case of particular medical domains, including real time data processing and feedback systems (Vasani et al., 2024)

In resource-limited settings, assisting physicians with disease identification can significantly improve patient outcomes. Early diagnosis is crucial, as many patients could remain healthy with timely intervention. (Zaidi et al., 2025)This research aims to develop a comprehensive system for the rapid and precise detection of endometriosis lesions. We explore the several deep transfer learning architectures, specifically MobileNetV2, VGG19, and InceptionV3, on the Gynecologic

Laparoscopy Endometriosis Dataset (GLENDA) (Zaidi et al., 2025). Through an extensive literature review and parameter optimisation, we find that MobileNetV2 outperforms the other models in terms of accuracy. However, challenges remain, as healthcare imaging datasets often suffer from limited sample sizes and uneven class distributions. Collecting additional samples can be costly and time-consuming, which is a prevalent issue in medical imaging. To address this, we employ Deep Convolutional Generative Adversarial Networks (DCGAN) to enhance the dataset by generating synthetic images, thus improving class balance. This image augmentation strategy not only boosts model performance but also reduces the manual effort required for image labelling. We evaluate our proposed model using metrics such as accuracy, precision, recall, and F1-score. Initially, our model achieves an accuracy of 95%. The introduction of synthetic samples results in an increased accuracy of 99%, reflecting a 4% improvement and enhancing the model's overall efficacy. (Zaidi et al., 2025)

Novel, deep learning, generative model named **Foresight** that uses **natural language processing** to perform **longitudinal forecasting** of patient timelines from electronic health records. The model, which is based on a **transformer-based architecture**, is designed to be highly scalable, allowing it to generate a patient's medical future from single time steps to multi-year chronic conditions with minimal modification. This temporal modelling capability has broad utility, including enabling "what if" scenarios for health digital twins and a pathway for counterfactual modelling to facilitate causal inference. The model can also be used for medical education by simulating realistic case studies, which allows students to practice clinical reasoning and decision-making in a safe, virtual environment. (Kraljevic et al., 2024)

Foresight is a general-purpose model for biomedical concept modelling that can be used for real-world risk forecasting, virtual trials, and clinical research to study the progression of disorders, to simulate interventions and counterfactuals, and for educational purposes.(Kraljevic et al., 2024)

- **Case study: NLP pipeline to detect undiagnosed endometriosis in large EHR datasets**

The use of an NLP pipeline to detect undiagnosed endometriosis in large EHR datasets is a promising strategy to address the significant diagnostic delay and misdiagnosis associated with the disease. While EHRs contain a wealth of information, relying on structured data like diagnostic codes and procedures alone can underestimate the prevalence of underdiagnosed conditions (Ravi et al., 2023). For diseases like endometriosis, the unstructured data found in clinical notes are critical for phenotyping. EHRs are rich sources of clinical health data that document a patient's health experience, including symptoms such as abdominal pain and heavy/irregular menstrual bleeding that are often reported prior to an official diagnosis. By leveraging NLP to integrate this information with structured data and patient-reported outcomes, researchers can use a retrospective approach to identify patterns of health history and symptoms (Ravi et al., 2023). This data-driven phenotyping can define disease subtypes and aid in establishing screening guidelines to help clinicians efficiently recognise and diagnose endometriosis in all patient populations, ultimately reducing inequities in care. (Ravi et al., 2023)

Electronic health records (EHRs) have been widely adopted as a data source in biomedical research. However, they remain a largely untapped source of data for endometriosis research(Penrod et al., 2023). EHRs capture diverse, real-world patient populations and care trajectories and can be used to learn patterns of underlying risk factors for endometriosis, which, in turn, can be used to inform screening guidelines to help clinicians efficiently and effectively recognise and diagnose the disease in all patient populations, reducing inequities in care. Here, we provide an overview of the advantages and limitations of using EHR data to study endometriosis. (Penrod et al., 2023)

3.3 Explainable AI for Diagnostic Support

Use of SHAP, LIME to provide interpretable risk predictions

Endometriosis is a highly diverse and complex disease. The analysis of comorbidities in endometriosis may provide a deeper insight into its multidimensionality and heterogeneity. The significant clinical variability in manifestations and responses to treatments may represent diverse plausible but presently unconfirmed pathogenesis pathways (Signorile et al., 2022). The results of this investigation are promising and showcase the potential of using machine learning to assist healthcare professionals in identifying patients with possible endometriosis and allow for more efficient screening procedures. The XGBoost classifier achieved an AUC of 0.725 on test data. At the same time, it showed sensitivity and specificity of 68.6% and 62.9%, respectively. Nonetheless, its low positive predictive value of 1.5% suggests that the model should be seen as an assisting tool, rather than the final decision maker for endometriosis diagnosis. Moreover, this study found that the top five most important features are age, infertility (Practice Committee of the American Society for Reproductive Medicine, 2012), and uterine fibroids (Uimari et al., 2021)
, anxiety (Laganà et al., 2017), and allergic rhinitis (Matalliotakis et al., 2012), which are comorbidities that have been previously found with significant frequency in women with endometriosis. (Tore et al., 2022)

In order to improve the unexplainable recommendation results in the field of medical recommendations, this paper proposes an explainable medical-recommendation system for age-related chronic diseases based on LIME (Chen et al., 2023). By combining the LIME explainable model with traditional classification algorithms and applying it in the medical field, the reasons for recommending results are explained on the basis of realising predictions related to chronic diseases in the elderly. In this study, the method was applied to data sets on heart disease and diabetes in elderly patients with chronic diseases(Chen et al., 2023). Firstly, the data sets were preprocessed and normalised to ensure that the data in the data set were true, effective, and available. Next, the sorted data sets were input into six commonly used classification-algorithm models, including decision tree, random forest, the linear-regression model, multilayer perceptron, the gradient-enhancement-tree algorithm, and naive Bayes, to propose recommendations for age-related chronic diseases. Finally, the processed data set and recommendation results were trained through the LIME model to obtain the reasons for the recommendation results and provide interpretations. (Chen et al., 2023)

- **Enhancing physician trust in AI-based triage tools**

  Artificial intelligence (AI) is often cited as a possible solution to current issues faced by healthcare systems. This includes the freeing up of time for doctors and facilitating person-centred doctor-patient relationships. However, given the novelty of artificial intelligence tools, there is very little concrete evidence on their impact on the doctor-patient relationship or on how to ensure that they are implemented in a way that is beneficial for person-centred care. Given the importance of empathy and compassion in the practice of person-centred care, we conducted a literature review to explore how AI impacts these two values. Besides empathy and compassion, shared decision-making and trust relationships emerged as key values in the reviewed papers. We identified two concrete ways that can help ensure that the use of AI tools has a positive impact on person-centred doctor-patient relationships. These are **(Bohr & Memarzadeh, 2020)**using AI tools in an assistive role and **(British Medical Association, 2022**)adapting medical education. The study suggests that we need to take intentional steps in order to ensure that the deployment of AI tools in healthcare has a positive impact on person-centred doctor-patient relationships. We argue that the proposed solutions depend on clarifying the values underlying future healthcare systems. (Sauerbrei et al., 2023)

4. Future Directions

The application of artificial intelligence (AI) in endometriosis research is rapidly evolving and presents significant opportunities to transform diagnosis, prognosis, and personalized disease management. Future investigations should focus on the development of multimodal AI frameworks that integrate heterogeneous data sources, including clinical symptoms, imaging findings, electronic health records (EHRs), genomic profiles, biomarker signatures, and patient-reported outcomes. Such integrated approaches have the potential to improve diagnostic accuracy and enable earlier disease detection compared with current single-modality methods (Acosta et al., 2022; Cetera et al., 2024).

One of the major barriers to the clinical implementation of AI models is the limited availability of large, standardized, and representative datasets. Future research should prioritize multicenter collaborations, international biobanks, and data-sharing initiatives that facilitate the generation of diverse datasets while maintaining patient privacy and regulatory compliance. The integration of structured and unstructured EHR data through advanced machine learning and natural language processing techniques may further enhance disease prediction, risk stratification, and clinical decision support (Penrod et al., 2023; Kraljevic et al., 2024).

The identification of reliable non-invasive biomarkers remains a critical research priority. Emerging evidence suggests that AI-assisted analysis of multi-omics datasets, including transcriptomics, proteomics, metabolomics, and microRNA profiles, may accelerate biomarker discovery and validation. Future studies should focus on combining biomarker panels with machine learning algorithms to develop highly sensitive and specific diagnostic tools capable of reducing the current dependence on invasive procedures (Brulport et al., 2024; Hudson et al., 2020).

Advances in deep learning and computer vision also hold promise for improving image-based diagnosis. Future AI systems may support automated lesion detection, disease staging, and surgical planning using ultrasound, magnetic resonance imaging, and laparoscopic images. However, extensive external validation across diverse populations and healthcare settings will be necessary before routine clinical implementation can be achieved (Zaidi et al., 2025; Zhao et al., 2024).

Another emerging area involves the integration of digital health technologies, wearable devices, and mobile health applications. Continuous symptom monitoring and real-time collection of patient-generated health data may provide valuable insights into disease progression, treatment response, and quality-of-life outcomes. AI-driven digital platforms could facilitate personalized care pathways while improving patient engagement and self-management (Parazzini et al., 2023; Zhang et al., 2025; Luz & Lima, 2025).

Despite these advances, challenges related to model transparency, algorithmic bias, data security, and ethical governance remain significant. Future efforts should emphasize the development of explainable AI systems that provide interpretable predictions and foster trust among clinicians and patients. Regulatory frameworks and clinical validation studies will be essential to ensure the safe, equitable, and responsible deployment of AI technologies in endometriosis care (Dungate et al., 2024; Sivajohan et al., 2022).

Ultimately, the convergence of artificial intelligence, precision medicine, digital health technologies, and biomarker-driven diagnostics has the potential to fundamentally reshape endometriosis management. Continued interdisciplinary collaboration among clinicians, biomedical researchers, data scientists, and healthcare policymakers will be essential for translating these innovations into meaningful improvements in patient outcomes and quality of life.

5.Conclusion

The integration of artificial intelligence and machine learning into endometriosis research represents a fundamental shift in how this highly enigmatic, multi-system disorder is screened, diagnosed, and ultimately managed. For decades, the gynaecological community has grappled with an unacceptable diagnostic latency that compromises patient quality of life, exacerbates mental health issues like anxiety and depression, and incurs massive socioeconomic costs globally. As this review compiles, the transition toward multimodal data platforms that synthesise symptom surveys, longitudinal electronic health record text, imaging metrics, and omics-level biomarkers demonstrates that computational methods can effectively untangle the highly heterogeneous clinical presentations of this disease.

Symptom-based classifiers and mobile health apps demonstrate that high-accuracy screening tools can be successfully deployed at the earliest stages of symptom onset. Concurrently, transformer-based clinical language models offer a highly scalable approach for identifying underdiagnosed or misclassified cases in large hospital registries. By capturing subtle data patterns that frequently elude front-line, non-specialist clinicians, these tools can substantially shorten the traditional 7-to-11-year diagnostic gap. Furthermore, by providing accessible, objective, and low-cost digital screening metrics, AI architectures hold immense potential to minimise geographic and socioeconomic health disparities, offering expert-level risk assessment to underserved populations and mitigating the diagnostic biases often experienced by minority ethnic groups.

However, moving from experimental validation to actual bedside implementation presents several technical and systemic hurdles. The current AI/ML landscape in endometriosis research remains fragmented, characterised by small-scale, single-centre studies that utilise highly variable patient recruitment methods. This lack of standardisation introduces significant selection bias, such as distinct clinical variations observed between patients sourced from online support networks and those from specialised tertiary care facilities, which directly reduces the generalizability of predictive models. Furthermore, the clinical adoption of these tools is strictly constrained by the traditional "black box" nature of complex deep learning systems. Without clear, interpretable frameworks like LIME or SHAP that precisely map how a network determines high-risk status, frontline physicians cannot confidently integrate AI recommendations into their clinical decision-making.

To achieve successful, large-scale clinical translation, future research must prioritise cross-institutional data standardisation. This requires widespread adoption of unified semantic ontologies, such as combining ICD and SNOMED-CT frameworks, to turn unstructured electronic medical data into interoperable data collections. Large-scale, prospective multi-centre validation studies are urgently required to test non-invasive biomarker panels and automated imaging segmentation tools across truly diverse patient populations. Ultimately, AI should not be viewed as a standalone replacement for clinical judgment, but rather as an assistive, interpretative partner. By resolving data silos and establishing explainable, transparent risk-stratification models, the medical community can foster a more equitable, prompt, and person-centred approach to managing endometriosis globally.

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