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RESEARCH ARTICLE

ENDOMETRIOSIS: A CANCER-MIMICKING DISEASE AND THE NEED FOR A TRANSLATIONAL PERSPECTIVE

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ABSTRACT: Endometriosis, defined by the presence of endometrial-like tissue beyond the uterine cavity, afflicts over 190 million young women worldwide and often significantly reduces quality of life. Despite being historically classified as a benign gynecologic disorder, endometriosis can mimic cancer in imaging findings, serum tumor markers, and molecular signature. Increasing evidence suggests endometriosis encompasses multiple biologic subtypes rather than representing a single uniform disease, which may explain divergent presentations, from extensive lesions in some patients with minimal pain to smaller implants in others with severe symptoms. Current management relies heavily on empirical hormonal therapies, repeated surgeries, and symptomatic treatment. Inadequate diagnostic tools and incomplete mechanistic understanding contribute to misdiagnosis, delayed intervention, and suboptimal outcomes. Without deeper elucidation of its complex biology, especially at the molecular level, substantial therapeutic breakthroughs will likely remain elusive. Notably, pathways commonly implicated in malignancy are aberrantly activated in ectopic endometrial tissue, driving proliferation, angiogenesis, and immune evasion. To address heterogeneous endometriosis phenotypes, a rigorous translational framework is essential. Through such structured investigation, novel data and non-hormonal therapies targeting core molecular events could emerge, reducing both protracted diagnostic timelines and lowering the incidence of overtreatment. In recognizing endometriosis as potentially comprising distinct pathologies under one umbrella, the field may advance truly individualized, biology-guided interventions.

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Impact statement: Endometriosis, affecting over 190 million people worldwide, displays clinical and molecular profiles that closely resemble malignancies. Framing endometriosis as a "cancer-mimicking" disease highlights why current models, diagnostic tools, and empirical therapies fail to adequately address prolonged diagnostic delays, high recurrence rates, and inconsistent treatment outcomes. This perspective advocates a structured translational approach, integrating meticulous preclinical validation, phase-appropriate clinical trials, and rigorous safeguards in artificial intelligence and biomarker development, to bridge critical gaps in understanding disease biology. Such a bidirectional pipeline, guided by real-world clinical feedback and clear mechanistic insights, aims to optimize pain management, fertility preservation, and overall disease control. Reconceptualizing endometriosis as a systemic condition with cancer-mimicking features underscores the urgency and the opportunity to develop targeted therapies beyond traditional hormonal suppression and empirical surgeries, ultimately enhancing patient quality of life worldwide.

Key words: *endometriosis; cancer-mimicking; molecular medicine; translational research.*

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INTRODUCTION

Endometriosis, broadly defined as the presence of endometrial glands and stroma outside the uterine cavity, affects over 190 million young women worldwide and severely compromises the quality of their lives (1-3). Historically considered predominantly gynecological, current evidence positions endometriosis as a multisystem disorder driven by inflammatory, hormonal, genetic, and neurobiological drivers (2-5). Notably, its capacity for tissue invasion, recurrence, and resistance to standard therapies has led many experts to characterize it as "cancer-mimicking," reflecting both its clinical severity and complex underlying biology. However, despite sharing several molecular and clinical features with malignant conditions, endometriosis itself is not classified as cancer. Nevertheless, endometriosis does carry a recognized, albeit relatively low, risk of malignant transformation, to endometriosis-associated ovarian cancer (EAOC) (6) with recent studies indicating approximately a two-fold increase in lifetime risk (from about 1% in the general population to roughly 2% in women with endometriosis) (7-9). Critically, it remains uncertain which patients with endometriosis are at risk of progressing to ovarian cancer. Endometriosis imposes a substantial lifelong burden on women, primarily because prolonged diagnostic delays, often exceeding seven years due to nonspecific symptoms and overlap with other conditions, mean that many affected individuals live for years unaware of their underlying disease (10). Furthermore, the absence of a unifying theory (spanning retrograde menstruation, stem-cell hypotheses, or coelomic metaplasia) limits our understanding of why endometriosis emerges in some individuals, or why disease trajectories are heterogeneous (10-17). Treatment remains largely empirical, involving hormonal suppression, analgesics, and repeated surgeries, offering only transient or partial relief (18). In parallel, emergent technologies, refined imaging, artificial intelligence diagnostics, and novel molecular biomarkers, offer potential (4, 18). Nevertheless, premature implementation of these technologies, especially AI-driven diagnostics, without sufficient biological understanding, risks embedding biases, exacerbating inequalities, or restricting accessibility for marginalized populations (19, 20). Therefore, a patient-centered translational framework becomes paramount, allowing rigorous biologic characterization to shape early-phase validations, rather than deploying large-scale AI-driven strategies that might misdirect care. Indeed, parallels between endometriosis and malignancy, including shared molecular pathways and invasive properties, highlight the necessity for strategic, stepwise integration of laboratory findings and clinical observations. Leveraging the concept of endometriosis as "cancer-mimicking," we illustrate how ambiguous pathogenesis, diagnostic uncertainty, and nonspecific treatments hinder patient outcomes. First examine immunologic and molecular mechanisms underlying these cancer-mimicking traits, emphasizing the importance of elucidating these pathways for targeted intervention development. Next, we propose a bidirectional translational framework, anchored by phase 0/preclinical studies and informed clinical trials, aiming to advance diagnostics, management, and, potentially, preventive strategies.

MATERIALS AND METHODS

This manuscript is a perspective rather than a systematic review. We conducted a structured literature search using PubMed to address three thematic queries: (i) clinical manifestations of cancer-mimicking features in endometriosis (Section Clinical Parallels), (ii) molecular pathways shared with malignancy (Section Molecular Parallels), and (iii) translational research gaps and unmet clinical needs (Section Gaps in Understanding). The search strategy included original research articles and comprehensive reviews published in English, French, Spanish and Italian, identified using combinations of predefined keywords ("endometriosis," "cancer mimicry," "molecular pathway," "translational research"). Identified articles underwent initial screening based on title and abstract. Subsequently, selected publications were reviewed and refined by author consensus, considering direct relevance to the specified thematic areas. This process resulted in the selection of 35 articles for Sections Clinical Parallels and Molecular Parallels each, and eight articles for Section Gaps in Understanding. The selected references were not intended to represent an exhaustive review but rather to illustrate critical clinical observations, molecular insights, and translational opportunities pertinent to this perspective.

CANCER MIMICRY

Clinical Parallels

Clinical evidence consistently indicates that endometriosis, particularly in complex or atypical presentations, closely mimics malignancy in clinical, biochemical, radiological, and pathological findings. This resemblance includes elevated tumor markers, invasive imaging characteristics, and lesions at atypical anatomical sites, complicating diagnostic accuracy and often leading to overtreatment.

Elevated Tumor Markers

A frequent diagnostic pitfall arises when markedly elevated tumor markers, such as CA-125 or CA-19.9, which ordinarily raise suspicions of gynecologic or gastrointestinal malignancies, occur in endometriosis patients. Numerous reports document significantly elevated CA-125 levels, sometimes surpassing 1000 U/mL, prompting urgent oncologic evaluations (21-25). For example, an extremely elevated CA-125 level of 1386.50 U/mL, coupled with a large ovarian mass, led directly to surgery under suspicion of ovarian cancer (25). Similar elevations of CA-125 or CA-19.9 are also observed in extrapelvic lesions, including subcutaneous and abdominal wall endometriosis (26, 27). Although indicative of malignancy, these elevations lack specificity, underscoring the need for cautious interpretation.

Imaging Findings Suggestive of Invasive Disease

Advanced imaging modalities, including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and even positron emission tomography (PET), frequently detect masses with irregular margins, heterogeneous enhancement, and restricted diffusion, hallmarks of malignancy (28-30). Reports describe "ill-defined," "stellate," or "irregular" soft-tissue masses with enhancement patterns indistinguishable from malignancies (31-33). For instance, bladder-infiltrating endometriosis has appeared on MRI as a heterogeneous, solid mass with restricted diffusion, closely resembling bladder carcinoma (34). Similarly, ovarian polypoid endometriosis has been misdiagnosed preoperatively as advanced carcinoma due to papillary structures, solid components, or extensive "peritoneal" disease (25, 30). Also lesions in atypical locations, such as beyond the pelvis, because of discrete enhancing lesions in the lumbar plexus (35) or renal parenchyma (36-38) have led radiologists to suspect nerve sheath or renal cell tumors, respectively.

"Metastatic" or Disseminated Disease Patterns

Beyond local invasion, endometriosis may present as multifocal implants throughout the peritoneum, bowel serosa, and omentum, mimicking peritoneal carcinomatosis (23, 24). Some cases include extensive nodularity, ascites, and pleural effusions, features characteristic of advanced intra-abdominal or thoracic malignancies (32, 39). Widespread peritoneal dissemination, as observed in polypoid endometriosis (26, 30, 34, 40, 41), can be mistaken for metastatic dissemination. Even endometriotic lymph node involvement has been reported, raising suspicion of metastatic carcinoma (30, 42). One report detailed extrapelvic endometriosis with progressive abdominal distension and cachexia, two clinical indicators that triggered an oncology referral for presumed metastatic cancer (24).

Overlapping Symptom Profiles

Endometriosis frequently manifests with alarming symptoms classically linked to malignancy, such as rectal bleeding, hematuria, or large bowel obstruction (36, 40, 43). Rectal bleeding and weight loss in conjunction with a rectal mass have led clinicians to suspect colorectal cancer (43). Likewise, recurrent hematuria and flank pain associated with ureteral or bladder involvement have initially suggested urological malignancies (34, 36, 37). Similarly, uterine bleeding and pelvic masses often suggest gynecological cancers; however, polypoid endometriosis can produce an indistinguishable clinical picture (25).

Extensive Surgical Intervention due to Suspected Malignancy

Cancer-mimicking presentations sometimes prompt surgeons to undertake aggressive interventions, including radical hysterectomy, bilateral salpingo-oophorectomy, bowel resection, or omentectomy (38, 39, 44). In one striking example, a patient was scheduled for hyperthermic intraperitoneal chemotherapy to address presumed pseudomyxoma peritonei, only for intraoperative findings to reveal endometriosis (24). Such extensive procedures carry considerable morbidity, particularly if a benign process is overtreated (27). Frozen-section biopsies may also fail to definitively exclude malignancy, reinforcing diagnostic confusion (24, 32, 42).

Histopathological Pitfalls

Pathologists also face challenges, particularly with atypical variants such as polypoid endometriosis, decidualized endometriosis, or Müllerianosis in lymph nodes (31, 43-47). These entities may demonstrate glandular crowding, papillary architectures, or cytologic atypia, making intraoperative differentiation from malignancy difficult (30-32, 46). Immunohistochemistry is frequently indispensable to confirm endometrial derivation and rule out higher-grade carcinomas or metastatic lesions (31, 35, 43, 48, 49). Thoracic endometriosis, in particular, poses diagnostic challenges distinct from pelvic lesions. Unlike pelvic endometriosis, which has been more extensively studied and characterized, thoracic endometriosis demonstrates unique clinical and histological features that set it apart. These differences include variations in lesion appearance, behavior, and tissue composition. In particular, there is growing recognition of the importance of stromal endometriosis, lesions composed predominantly of endometrial-type stromal cells without accompanying glands, in the thoracic cavity. This form of endometriosis may be underdiagnosed or misclassified due to its subtle histological presentation, contributing to inconsistencies in diagnosis and classification across different anatomical sites. Understanding the distinct nature of thoracic endometriosis, especially the role of stromal components, is essential for improving diagnostic accuracy, guiding treatment strategies, and advancing a more comprehensive understanding of the disease's pathophysiology (50).

Clinical Consequences and Need for Vigilance

Taken together, these clinical and radiological parallels have significant implications for patient care. Suspicion of cancer prolongs diagnostic workups, increases patient anxiety, and may result in excessive therapy. Conversely, dismissing endometriosis prematurely may delay essential interventions and allow disease progression (24, 28, 37, 40, 46, 51). Consequently, clinicians should maintain a high index of suspicion for endometriosis in atypical presentations, extrapelvic masses, or cancer-like imaging profiles, regardless of reproductive age.

Clinical observations across multiple organ systems (21-49, 51-56) illustrate how endometriosis can reliably mimic malignancy, with raised tumor markers, suspicious radiographic features, multifocal dissemination, and deceptive histology (**Table 1**). These overlapping features underline the urgent need for enhanced education, training, and effective dissemination of existing diagnostic criteria for endometriosis. Treatment strategies should consistently adopt a multidisciplinary approach, applying current guidelines appropriately yet adapting them individually to each patient's specific clinical presentation, disease phenotype, and personal therapeutic objectives.

Table 1. *Endometriosis Mimicking Malignancy in 35 References.*

REFERENCE	SUSPECTED MALIGNANCY	LOCATION OF ENDOMETRIOSIS	CLINICAL CASE SCENARIO
Hu, 2021	Primary rectal aden\ ocarcinoma	Deep rectal wall/ rectosigmoid colon	Clinical: Rectal bleeding, weight loss Imaging (CT/MRI/EUS): 4.5–5 cm rectal mass (T3/T4 suspicion), restricted diffusion Pathology: Rectal Mucosal Biopsies showed mucosal hemorrhage with associated hypercellular stroma; Scattered atypical glands were present deep in the muscularis mucosa, rimmed by hypercellular stroma; The deep glands and surrounding stroma were strongly positive for Estrogen Receptor: The cellular stroma was strongly positive for CD10 3; These histological and immunohistochemical findings confirmed the diagnosis of endometriosis
Stuparich, 2020	Peritoneal carcinomatosis/ Gynecologic malignancy	Multiple peritoneal nodules, abdominal wall, omentum	Clinical: Postmenopausal on estrogen Imaging (CT): Multiple nodules suspicious for carcinomatosis Laparoscopy: Irregular nodules, neovascularization Pathology: An initial CT-guided biopsy demonstrated endometriosis, but malignancy could not be definitively excluded. Intraoperative pathology during the laparoscopic procedure demonstrated only endometriosis. The final pathology report, after the surgical removal of all disease, showed polypoid endometriosis without cancer.
Gargan, 2023	Ovarian malignancy (multiple solid masses)	Right ovary (adjacent to endometrioma)	Clinical: Premenopausal, worsening pelvic pain Imaging (US/MRI): Several solid, echogenic, vascular lesions with homogeneous enhancement Pathology: Polypoid endometriosis mimicking neoplastic masses

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REFERENCE	SUSPECTED MALIGNANCY	LOCATION OF ENDOMETRIOSIS	CLINICAL CASE SCENARIO
Kaymaz Gezer, 2016	Malignant mesothelioma (deciduoid) in differential	Cesarean section scar (abdominal wall)	Clinical: Mass in previous C-section scar Pathology: Decidualized endometriosis with large polygonal cells resembling deciduoid mesothelioma
Mota, 2020	Colorectal cancer	Upper rectum, middle sigmoid colon	Clinical: Changes in bowel habits, intermittent hematochezia Imaging (CT): Irregular parietal thickening with contrast enhancement, stenosis Colonoscopy: Concentric stenosis, friable mucosa (negative biopsies) Pathology: proctosigmoidectomy specimen revealed intestinal wall endometriosis, compromising submucosa and internal and external muscular layers, with fibrosis.
Sarofim, 2018	Primary sigmoid malignancy	Distal sigmoid colon, rectum, pericolic LNs	Clinical: Acute large bowel obstruction Imaging (CT): Thickened distal sigmoid mass causing obstruction Operative: Dense adherence to pelvic sidewall Pathology: Endometriosis in pericolic nodes mimicking metastatic spread
Rodrigues, 2015	Recurrent perianal abscess/fistula (non-malignant)	Perianal region (episiotomy scar)	Clinical: Anal itching, pain, discharge Endorectal US: Irregular hypoechoic lesion Pathology: Confirmed perianal endometriosis
Uno, 2014	Nuck cyst/ femoral hernia (benign differential)	Right groin (femoral ring)	Clinical: Painful, enlarging groin mass Imaging (MRI): Cystic structure with hemorrhagic features, elevated CA-125 Histology: Mesothelial cyst with endometrial stroma
Foulon, 2021	Crohn's disease (perforating)	Bowel (ileum, colon), pelvis	Clinical: Diarrhea, abdominal pain, abscesses Imaging: Ileitis, colitis, multiple abscesses, sigmoid stricture. Magnetic Resonance Imaging (MRI): Revealed findings more characteristic of endometriosis, such as sigmoid wall thickening with infiltration of the perisigmoid fat, adhesions, a retractile endometrial nodule, and a left endometrioma 1. Computed Tomography (CT) Colonography: Confirmed the sigmoid stricture but also showed nodular lesions in the mesorectum, compression of the left ureter by a nodule, a right ovarian cyst, and a small left ovarian cyst 1. Endoscopic Sonography of the Rectum: Showed a 32 mm lesion that was suggestive of rectal endometriosis Labs: Elevated CRP/WBC; actually, endometriosis mimicking Crohn's disease Diagnosis: Based on these collective imaging findings (MRI, CT colonography, Endoscopic Sonography), which revealed features highly suggestive of endometriosis (endometrial nodule, endometrioma, specific lesions, ovarian cysts), the clinical team changed the diagnosis from Crohn disease to complicated deep endometriosis
Kourouma, 2017	Keloid (though malignancy sometimes considered)	Umbilicus (cutaneous)	Clinical: Painful, enlarging umbilical nodule on dark skin Initially treated with steroids as keloid Cyclical bleeding indicated endometriosis Pathology: Under an ulcerated epidermis, the presence of endometrial glands lined by cylindrical epithelium was observed. Endometrial stroma composed of small round cells was also present.
Mahiou, 2024	Invasive pelvic cancer (gynecologic or colorectal)	Vaginal stump, rectovaginal septum, rectum, pelvic peritoneum	Clinical: 68-year-old postmenopausal, infiltrating vaginal stump mass MRI: Solid + cystic lesion, hemorrhagic components Intraop: Cauliflower-like mass; extensive resection Pathology: Endometriosis
Carvalho, 2020	Ovarian/ peritoneal malignancy	Retroperitoneal mass (17x13x16 cm), omen tum, iliac LN	Clinical: 31 y/o, large solid-cystic massCA-125: 641 U/mL Laparoscopy: Frozen pelvis, suspicious omental nodules Pathology: Hard, irregular lesion resembling tumor; final = endometriosis

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REFERENCE	SUSPECTED MALIGNANCY	LOCATION OF ENDOMETRIOSIS	CLINICAL CASE SCENARIO
Fischer, 2021	Invasive carcinoma (florid mesothelial hyperplasia)	Abdominal wall (Pfannenstiel incision)	Clinical/Path: Endometriosis with florid mesothelial hyperplasia Pathology: Florid mesothelial hyperplasia occurring within fibrous tissue associated with abdominal wall endometriosis. The lesion exhibited an infiltrative pattern and stellate architecture, mimicking an invasive carcinoma, particularly given its cytokeratin positivity 1, 2. However, the mild cytologic atypia and positive staining for mesothelial markers (calretinin, WT-1, CK5), along with negativity for markers typical of common adenocarcinomas, established the diagnosis as a benign, reactive mesothelial proliferation.
Pang, 2019	Advanced ovarian cancer	Uterus (posterior fundus), bilateral ovaries, peritoneum	Clinical: Weight loss, large pelvic massCA-125: 372.4 U/mL Imaging: Solid/cystic tumor, 2000 mL bloody ascites Pathology: Endometriosis
Rodriguez, 2017	Cervical adenocarcinoma (Pap smear AGC-NOS)	Cervix (superficial endometriosis)	Clinical: Atypical glandular cells on Pap(AGC-NOS) Concern for endocervical neoplasia Pathology: Microscopically, glandular formations with an endometrial pattern were found, surrounded by fibrous stroma. These findings were suggestive of an endometrioma
Yang, 2021	Cystic renal tumor (Bosniak III)	Lower pole of right kidney	Clinical: Intermittent gross hematuria Imaging (CT/US): Complex cystic renal mass (50% chance of malignancy) Pathology: Histopathology revealed endometriosis of the right renal parenchyma. Gross Examination: The resected mass had a diameter of approximately 1.5 cm. It contained several capsular spaces filled with brown fluid, and the cut surface of the mass was yellowish. Microscopic Examination: Confirmed the diagnosis of renal endometriosis, characterized by the presence of endometrial glands and embedded stromal cells. No atypia was observed. Im immunohistochemical Analysis: The stromal cells and epithelial cells were positive for estrogen receptor (ER), progestin receptor (PR), and vimentin, further supporting the diagnosis of renal endometriosis.
Basnayake, 2020	Possible malignant transformation of inguinal endometriosis	Inguinal canal	Clinical: 4x4 cm cystic mass in inguinal region Imaging: Benign hydrocele-like, unusual site Surgery to exclude malignancy; Pathology: Endometriosis
Molina, 2019	Cecal/colorectal cancer	Cecum, right adnexa	Clinical: Acute complete bowel obstruction, weight loss, mass Imaging: 7x7x4 cm cecal lesion + adnexal mass High suspicion of malignancy Pathology: Ce cum Mass: A 4 × 3 × 2.5 cm bluish, heterogeneous mass was identified, which occluded almost all the lumen of the cecum and the ileocecal valve. Microscopic Examination (Cecum): Microscopy showed that the colon wall was invaded by glands and endometrial stroma. The colonic epithelium displayed inflammatory changes but was negative for malignancy. Adnexal Mass (Ovary and Fallopian Tube): In the ovarian parenchyma, an endometrial cyst covered with siderophages was found. Glands and endometrial stroma were also observed in the fallopian tube. The final diagnosis based on these findings was endometriosis
Hsieh, 2023	Intra-abdominal malignancy (gynecologic)	Within uterine leiomyoma + peritoneum	Clinical: Large (~10 cm) heterogeneous tumor, ascites, severe pain CA-125: 3061, CA-19.9: 1407 Ruptured lesion with suspicious implants; Pathology: Endometriosis

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REFERENCE	SUSPECTED MALIGNANCY	LOCATION OF ENDOMETRIOSIS	CLINICAL CASE SCENARIO
Cameron, 2016	Metastatic breast carcinoma	Umbilicus (subcutaneous)	Clinical: Postmenopausal with prior invasive lobular breast CA New umbilical lesion suspicious for metastasis Pathology: Endometriosis
Yazawa, 2022	Advanced ovarian carcinoma	Right adnexa, cecum, sigmoid, omentum	Clinical: Rapid tumor growth, partial obstruction Imaging (CT/PET): Multiple solid masses, high FDG uptake Pathology: Disseminated endometriosis
Gaillard, 2022	Peritoneal surface malignancy (mesothelioma, ovarian CA)	Diffuse intraperitoneal cystic lesions, mesentery, pelvic peritoneum	Clinical: Progressive abdominal distention, cachexia Imaging: Multicystic peritoneal disease, hydronephrosis Elevated CA-125, CA-19.9; Pathology: Laparoscopic Appendectomy (Age 23): The specimen was negative for appendicitis, endometriosis, or an appendiceal neoplasm. Diagnostic Laparoscopy (Age 26): Biopsies of diffuse cystic lesions revealed abdominal cysts but were negative for endometriosis. Cytologic Examination (Age 29, from drained cyst fluid): Revealed neutrophil granulocytes (indicating infection/inflammation). Cultures were positive for Staphylococcus aureus. Diagnostic Laparoscopy (Age 29): Biopsies of a cystic wall showed fibrinoid tissue and macrophages loaded with hemosiderin (indicating clearance of old hemorrhage). These were negative for endometriosis and malignant disease. De bulking Surgery (Age 29): Frozen Section: Analysis of a sample from the wall of the largest cyst revealed numerous hemosiderin loaded macrophages. No malignancy was present in this sample. Final Histology (Post Debulking): Confirmed the presence of a large cyst (32 × 16 × 5 cm) and multiple smaller cysts containing endometrial epithelium and specialized stroma, consistent with endometriosis. Stripping specimens showed mesothelium and the presence of pigmented macrophages. Cytologic analysis revealed ligated blood cells without malignant cells.
Buder Bakhaya, 2019	Metastatic melanoma	Subcutaneous tissue, lower right abdomen	Clinical: History of melanoma, new subcutaneous lesion Imaging (MRI): Solid lesion with enhancement Pathology: Endometriosis
Iida, 2017	Ovarian carcinoma(with LN metastasis)	Left ovary (polypoid endometriosis), pelvic LN	Imaging (MRI): Papillary nodules, diffusion restriction Enlarged LN with strong enhancement Elevated CA-125, CA-19.9; malignancy not excluded intraop; Pathology: Endometriosis
Jeswani, 2011	Nerve sheath tumor (schwannoma)	Left L4 neural foramen	Clinical: Progressive radicular pain Imaging (MRI): Foraminal mass, suspected schwannoma Intraoperative: Mass involving nerve root; Pathology: endometriosis
Takeda, 2025	GIST, schwannoma, glomus tumor, or metastatic cancer	Terminal ileum/ ileocecal region	Clinical: Intestinal obstruction Imaging (CT, colonoscopy): Well-enhanced submucosal mass, inconclusive biopsies Pathology: Endometriosis
Badri, 2018	Renal malignancy	Upper pole of left kidney	Clinical: Flank pain, gross hematuria Imaging (CT/MRI): Heterogeneous enhancing renal mass Pathology: Robotic partial nephrectomy: Endometriosis
Nambiar, 2018	Metastatic breast carcinoma	Abdominal wall (sub cutaneous), suprapubic region	Clinical: Advanced breast CA; new abdominal wall mass Pathology: Endometriosis, not metastatic disease
AlSinan, 2021	Inguinal hernia *vs.* Malignant soft tissue tumor or lymphoma	Left inguinal region (round ligament)	Clinical: Painful, cyclical inguinal mass Imaging: Solid inguinal lesion Differential: Sarcoma, lymphoma; Pathology: Endometriosis

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REFERENCE	SUSPECTED MALIGNANCY	LOCATION OF ENDOMETRIOSIS	CLINICAL CASE SCENARIO
Wu, 2023	Colorectal cancer	Sigmoid colon, peri colic LNs	Clinical: Large-bowel obstruction, weight loss, constipation Imaging: Mural thickening, impassable steno sis Pathology: Macroscopic Findings: The specimen showed localized, rubbery bowel wall thickening which was compressing and distorting the lumen. The serosa appeared mottled brown, indicating previous hemorrhage and hemosiderin deposition, and also showed greyish-white fibrous puckering. A cross section showed a rubbery, pale tan appearance consistent with hyperplastic smooth muscle compressing the lumen. Patches of congested, mottled, and brown serosa overlay sites of endometriosis. No features suggestive of malignant transformation were found . Microscopic Findings: The presence of endometrial glands and stroma scattered throughout the bowel wall (submucosa and muscularis propria) confirmed the diagnosis of Deep Infiltrating Endometriosis (DIE). There was marked smooth muscle hyperplasia, expanding the bowel wall. The muscularis mucosae was seen blending with the muscularis propria, and the hyperplastic smooth muscle contained scattered endometrial-type glands. Ectopic endometrial epithelium was discovered within two pericolic lymph nodes. Within the affected lymph node(s), there was a cystically dilated gland lined by endometrial epithelium, contain ingblood/fibrin, surrounded by lymph node parenchyma showing reactive follicles.
Ledezma, 2021	Bladder malignancy	Bladder dome (infiltrating), contacting remnant cervix & sigmoid	Clinical: Chronic pelvic pain, severe hematuria Imaging (US/CT/MRI): Infiltrative bladder mass, restricted diffusion CA-125: 93.9 Pathology: Endometriosis
Medlin, 2016	Pseudomyxoma peritonei (appendiceal/ peritoneal CA)	Diffuse peritoneal implants, large cystic masses, endometriomas	Clinical: Diffuse abdominal pain, weight gain, ascites Imaging (CT): Multi-loculated fluid, bowel centralization, adnexal mass Elevated CA-125 (223) Pathology: Endometriosis
Fan, 2025	Ovarian/ peritoneal malignancy	Left ovary (polypoid endometriosis), pelvic side wall, uterus, right adnexa	Clinical: Severe pelvic pain, recurrence Imaging (CT/ MRI): Complex cystic-solid pelvic masses, infiltration, hydronephrosis CA-125: 1386.5 Pathology: Polypoid endometriosis
Zhao, 2018	Rectal cancer; also suspected cervical cancer or GIST	Rectal wall (4 cm from anus)	Clinical: Postcoital bleeding, constipation, narrow stool Imaging (US, CT, PET): Rectal mass with FDG uptake Initial biopsy: Mesenchymal tumor suspicion; Pathology: Endometriosis
Umair, 2020	Renal tumor	Right kidney (interpolar region)	Clinical: Paroxysmal flank pain in pregnancy Imaging (MRI): ~ 6 cm heterogeneous renal mass Radical nephrectomy for presumed malignancy; Pathology: endometriosis

Molecular Parallels

Clinical reports indicating that endometriosis frequently mimics cancer in its presentations have found corroboration at the molecular level, where substantial parallels have emerged. Multiple canonical malignancy-associated pathways (PI3K/AKT/mTOR, MAPK (ERK, p38, JNK), NF-κB, Wnt/β-catenin, and JAK/STAT) demonstrate aberrant activation in endometriotic lesions. These similar pathways sustain proliferation, invasive capacity, angiogenesis, and an anti-apoptotic state, fostering an environment in which endometriosis can behave much like a neoplasm although endometriosis does not fulfill all the hallmarks of cancer (57). Further amplifying these malignant-like behaviors are hormonal signaling disturbances (notably estrogen-dependent growth and progesterone resistance), persistent inflammatory drivers, and various epigenetic modifications often also implicated in tumor pathogenesis **(Figure 1)**.

Molecular Pathways

- PI3K/AKT/mTOR Pathway: Extensive work has established that the PI3K/AKT/mTOR axis is persistently overactive in eutopic and ectopic endometrial cells, evidenced by high levels of phosphory-

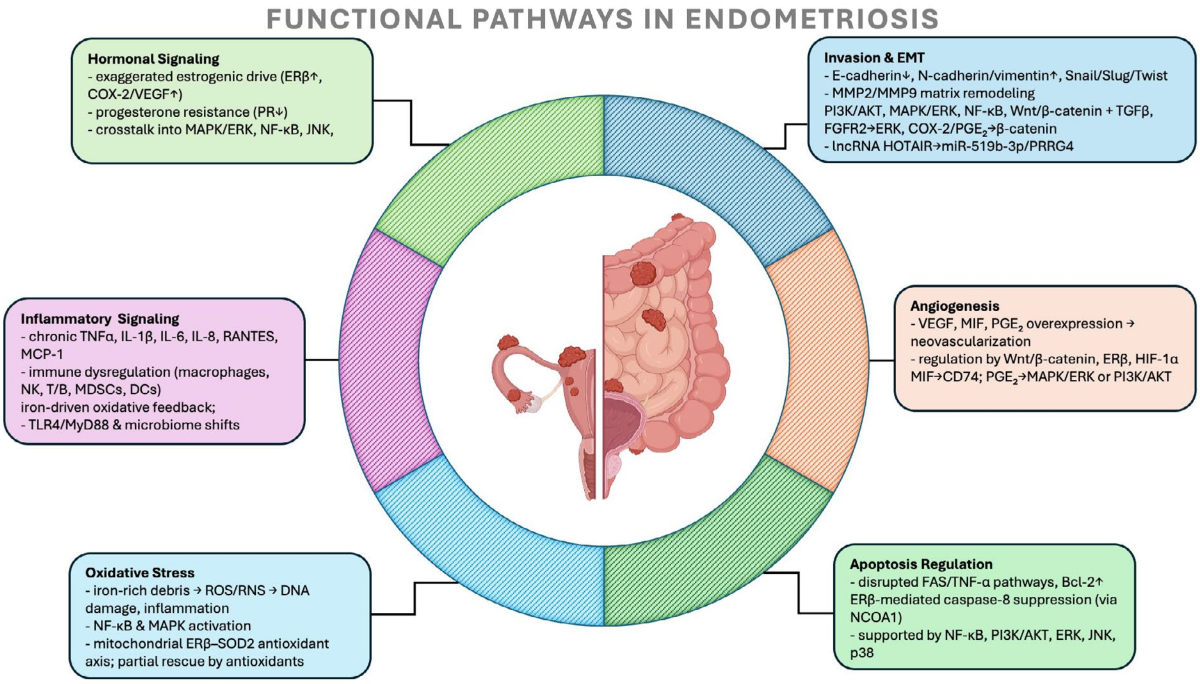

Figure 1. *This figure highlights six interrelated functional pathways that underlie the pathophysiology of endometriosis, depicted around a central image showing ectopic endometrial lesions dispersed across pelvic and intestinal structures. Each color-coded sector summarizes evidence-based mechanisms contributing to lesion establishment and survival:*

- ***Hormonal Signaling***
  Exaggerated estrogenic drive (elevated ERβ expression, COX-2/VEGF induction) and reduced progesterone receptor signaling jointly sustain inflammatory and proliferative cascades, in part through crosstalk with MAPK/ERK, p38, NF-κB, JNK, and Wnt/β-catenin (59, 70, 71, 75, 78).
- ***Inflammatory Signaling***
  Persistent elevation of proinflammatory cytokines (TNFα, IL-1β, IL-6, IL-8, RANTES, MCP-1) and immune cell dysregulation (macrophages, NK cells, T/B lymphocytes) drive lesion progression and pain. Iron overload from retrograde menstruation intensifies oxidative damage, while TLR4/MyD88 and microbiome shifts exacerbate localized and systemic inflammation (59, 69, 71, 78, 81-83).
- ***Oxidative Stress***
  Repeated hemorrhage into the peritoneal cavity and iron-rich debris trigger excess reactive oxygen/nitrogen species, fueling DNA damage and inflammation. Mitochondrial ERβ-mediated responses, along with NF-κB and MAPK activation, reinforce lesion viability; partial amelioration is possible through antioxidant strategies in model systems (65, 67, 69, 71, 75, 78, 84).
- ***Apoptosis Regulation***
  Aberrations in FAS and TNF-α pathways, coupled with increased Bcl-2 expression, enable endometriotic cells to evade apoptosis. Multiple pathways, including NF-κB, PI3K/AKT, ERK, JNK, and p38, further sustain cell survival, while mitochondrial ERβ can suppress caspase 8 (via NCOA-1), mirroring chemoresistance observed in malignancies (59, 69, 71, 78, 85).
- ***Angiogenesis***
  Overexpression of VEGF, MIF, and PGE_2 drives formation of new vascular networks critical for lesion nourishment. Regulation by Wnt/β-catenin, ERβ, and HIF-1α converges on MAPK/ERK and PI3K/AKT/mTOR, while NF-κB signaling amplifies the production of pro-angiogenic mediators (69, 71, 83, 85).
- ***Invasion and Epithelial–Mesenchymal Transition (EMT)***
  Decreased E-cadherin and heightened markers such as N-cadherin and vimentin, together with Snail/Slug/Twist transcription factors, promote tissue invasion and migration. Mechanistic drivers, PI3K/AKT, MAPK/ERK, NF-κB, Wnt/β-catenin, act in concert with TGFβ and COX-2/PGE_2, while lncRNA HOTAIR fosters EMT through miR-519b-3p/PRRG4 (59, 60, 68-70, 76).

lated AKT (p-AKT), PI3K, AKT1, 4EBP1, and mTOR-activating proteins (AXL, SHC1), together with diminished PTEN-mediated inhibition (58–64). Notably, hotspot mutations in *PIK3CA* and *PTEN* have been reported in deep infiltrating variants, implicating these genetic defects in advanced disease. Through this pathway, endometriosis lesions gain proliferative, pro-angiogenic, and pro-survival functions, potentially contributing to both progesterone resistance and heightened risk of EAOC (58-65). Regulatory control is multifactorial: cytokines (TNFα), growth factors (FGFR2, ERBB2/3), and estrogen (via PTEN suppression) jointly activate PI3K/AKT. Non-coding RNAs such as miR-92a and miR-135a/b further amplify the pathway, whereas miR-194-5p attenuates it. LncRNAs, notably HOXA-AS2, interface with miR-4459/IGF2BP2 to enhance cell proliferation via AKT, and ENPP3, commonly hypomethylated, fuels the AKT/mTOR/4EBP1 axis. In addition, endostatin-expressing endometrial stem cells may counter angiogenic signals via miR-21-5p/TIMP3 within this cascade (58, 60-62, 62-64, 66).

- MAPK Pathways (ERK, p38, JNK): Enhanced activation of ERK, p38, and JNK MAPKs is evident in endometriotic lesions relative to normal endometrial tissue (59, 67, 68). These MAPKs govern proliferation, survival (through Bcl-2), migration, invasion, angiogenesis, inflammation, and pain hypersensitivity. Their activation arises from diverse stimuli, TNFα, IL-1β, FGFR2, leptin, or TGFβ, and proceeds via the Ras–Raf–MEK cascade (59, 62, 66). Specific miRNAs (e.g., miR-340-5p) modulate MAPK activity and pharmacological inhibition of Raf, VEGFR, p38, or JNK suppresses lesion growth in preclinical models (55, 64).

- NF-κB Pathway: Chronic NF-κB activation occurs in ectopic stromal cells and peritoneal macrophages, diverging from normal cyclic regulation (61, 69). This persistent activation drives inflammatory mediators (IL-6, IL-8, RANTES, MCP-1, GM-CSF, MIF), matrix remodeling via metalloproteinases (MMPs), angiogenesis (VEGF), and resistance to apoptosis (59, 61, 62, 65, 66, 69, 70). NF-κB activation is triggered by TNFα, IL-1β, TSLP, iron overload, or TLR4/MyD88 signaling, whereas miR-16 negatively regulates the pathway by targeting IKKβ (65, 66, 69, 71).

- Wnt/β-catenin Pathway: Aberrant Wnt/β-catenin signaling in endometriosis, characterized by altered β-catenin expression and SFRP2 hypomethylation, promotes invasive growth, fibrosis, and epithelial–mesenchymal transition (EMT) (65, 72, 73). Progesterone usually inhibits Wnt/β-catenin, but progesterone resistance diminishes this protective effect. Dysregulated factors (estrogen, FOXP1, WEE1, MMP9) sustain Wnt signaling, while miRNAs (miR-33b, let-7a/g, miR-532-3p) and COX-2/PGE2 influence pathway intensity and EMT induction (58, 70, 71, 73).

- JAK/STAT Pathway: Research focusing on the JAK2/STAT3 arm identifies IL6ST (gp130) hypomethylation and overexpression in ectopic tissue, magnifying IL-6 signaling (74). Enhanced JAK2/STAT3 contributes to lesion proliferation, invasion, and anti-apoptotic phenotypes analogous to tumorigenic growth (74). Simultaneously, downregulation of STAT1 by miR-194-5p removes a moderating effect on mTOR, further bolstering JAK2/STAT3 (58, 74).

- Epigenetic and Non-coding RNA Regulation: The role of epigenetic derangements, DNA methylation shifts (e.g., SFRP2 hypomethylation or aberrant IL6ST methylation), histone modifications (HDAC upregulation), and dysregulated miRNA/lncRNA expression, in driving ectopic lesion resilience (64, 65, 72, 74–76) have been raised attention. Genes mediating steroid hormone action (ESR2, PR), inflammatory signaling (IL6ST), or tumor suppression (RASSF1A, E-cadherin) are frequently abnormally silenced or expressed. As seen in oncologic processes, such epigenetic alterations provide cellular plasticity, allowing endometriotic lesions to endure fluctuations in hormones and cytokines. Concomitant aberrations in specific miRNAs (e.g., miR-135b or miR-194-5p) or lncRNAs (HOXA-AS2, HOTAIR) can intensify these adaptive capabilities (64, 65, 71, 74, 74-79).

Critical Functional Modifications

- Hormonal Signaling (Estrogen/Progesterone): Endometriosis characteristically shows an exaggerated estrogenic drive and impaired progesterone receptor signaling, driving persistent lesion growth and inflammatory responses (59, 71, 75, 77, 78, 80). Notably, ERβ is abundant, even within mitochondrial compartments, supporting enhanced bioenergetics and oxidative stress defenses. Estrogen triggers COX-2 and prostaglandin upregulation, as well as angiogenic mediators (VEGF), while progesterone resistance, encompassing reduced PR expression, disrupts physiologic tissue remodeling (59, 70, 71, 75, 77). Hormonal crosstalk also activates MAPK/ERK, p38, NF-κB (through PTEN attenuation), JNK (via TSLP), and Wnt/β-catenin, with epigenetic modifiers such as Betulinic Acid (ERβ suppression) and miR-23a/b (SF-1) further refining these networks (59, 66, 67, 69).

- Inflammatory Signaling: Chronic inflammation remains a hallmark of endometriosis, reflected by heightened TNFα, IL-1β, IL-6, IL-8, RANTES, and MCP-1 in peritoneal fluid and lesions. Concomitant dysfunction occurs in macrophages, NK cells, T and B cells, MDSCs, and dendritic cells (59, 69, 71, 77, 81-83). This proinflammatory milieu helps establish lesions, promotes new vessel formation, and drives fibrosis and pain. Iron overload arising from retrograde menstruation can intensify inflammatory and oxidative damage, while broad molecular routes (NF-κB, MAPK, JAK/STAT, PI3K/AKT/mTOR) orchestrate extended neuroinflammatory cascades. Moreover, gut microbiome shifts and TLR (TLR4/MyD88) perturbations appear to escalate systemic and localized inflammation (59, 69, 71, 77, 81-83).

- Oxidative Stress Pathway: Repeated episodes of retrograde bleeding deposit iron-rich debris, fueling reactive oxygen and nitrogen species that injure DNA, heighten inflammation, and potentially initiate precancerous changes (65, 69, 71, 75). Mitochondrial ERβ may modulate aspects of antioxidant responses (e.g., SOD2). Chronic oxidative stress reciprocally activates NF-κB and MAPK, reinforcing lesion viability. Model systems demonstrate that antioxidant interventions can partially mitigate these detrimental effects (66, 69, 75, 77, 84).

- Apoptosis Regulation: Another defining feature is the ability to evade programmed cell death through disrupted FAS or TNF-α–mediated pathways, bolstered by elevated Bcl-2 (59, 69, 71, 85). This evasion allows ectopic tissue to persist through cyclical hormonal changes. Investigations underscore pivotal roles for NF-κB, PI3K/AKT, ERK, JNK, and p38 in maintaining these cells, while estrogen (ERβ) can suppress caspase 8 by means of cofactors such as NCOA-1 (59, 69, 71, 77). Such anti-apoptotic mechanisms mirror chemoresistance in various malignancies.

- Angiogenesis: Multiple studies reveal that VEGF, MIF, and PGE2 are consistently overexpressed in endometriosis, forming an aggressive neovascular network critical for lesion support (69, 71, 83, 85). This shift into enhanced vessel formation mirrors tumor biology, delivering nutrients and oxygen to ectopic cells. Wnt/β-catenin, ERβ, and HIF-1α can govern VEGF expression, whereas MIF (acting via CD74) and PGE2 converge on MAPK/ERK or PI3K/AKT/mTOR routes (69, 71, 83, 85). NF-κB likewise induces pro-angiogenic mediators.

- Cell Invasion, Migration, and EMT: Endometriotic tissue often manifests lowered E-cadherin, heightened N-cadherin and vimentin, and transcription factors (Snail, Slug, Twist) that define EMT (67-69, 71-73, 86). Metalloproteinases, such as MMP2 and MMP9, remodel extracellular matrices, fostering deeper tissue infiltration. These invasive traits are orchestrated by pathways including PI3K/AKT, MAPK/ERK, NF-κB, and Wnt/β-catenin, often with TGFβ serving as a central pro-invasive factor. FGFR2 augments migration via ERK, while COX-2/PGE2 interacts with β-catenin. LncRNA HOTAIR drives EMT through miR-519b-3p/PRRG4, aligning with malignant-type metastatic processes (59, 60, 67-70, 76).

GAPS IN UNDERSTANDING

Despite substantial progress in elucidating clinical and molecular aspects of endometriosis, significant uncertainties persist regarding its pathogenesis, accurate diagnosis, and effective application of emerging insights to patient care.

Methodological and Translational Limitations

Numerous research teams emphasize the shortcomings of existing in vitro and in vivo models, which fail to mirror the complexity of the human disease. Most rodent models insufficiently capture the varied pain phenotypes, particularly non-evoked, chronic components, that characterize endometriosis in patients. While such models remain key to preclinical testing, they often focus on reflex-based endpoints alone, thereby underrepresenting clinically relevant pain features (87). Furthermore, many preclinical and clinical studies inadequately or inconsistently address pain endpoints, limiting translational relevance (88). Parallel issues exist in the validation and clinical translation of biomarkers. Although numerous genomic, epigenomic, proteomic, and metabolomic candidates have been proposed, few have demonstrated sufficient sensitivity, specificity, or reproducibility to enter clinical practice reliably (89). Variability across studies, limited sample sizes, and a lack of robust validation studies prevent broader implementation, leaving invasive diagnostic methods and empirical management as current standards of care (90).

Clinical Challenges and Unmet Needs

Pain Mechanisms: A crucial unresolved issue is the poor correlation between lesion burden and pain severity; some patients experience minimal symptoms despite extensive disease, while others suffer severe, debilitating pain from minor lesions. Emerging evidence suggests that neuroinflammatory pathways and central sensitization mechanisms might decouple pain from lesion size or anatomical staging (91). As conventional surgical or hormonal therapies target primarily visible lesions, many patients remain undertreated for persistent or recurrent pain. Without clearer insights into these overlapping neuronal and inflammatory processes, current approaches may miss a substantial subset of patients who continue to experience pain despite standard treatments.

Lesion Biology Heterogeneity: Significant variability in lesion morphology, invasive behavior, hormonal responsiveness, and recurrence risk underscores inherent biological heterogeneity in endometriosis. Evidence suggests stem-like or progenitor cell populations contribute substantially to lesion resilience and therapeutic resistance (92). However, direct identification of these stem-like cells in clinically pertinent models, particularly for deep infiltrating endometriosis, is lacking. Improved techniques to isolate and characterize such cells could enable more precisely targeted therapies that reduce recurrence without the broad side effects characteristic of hormonal suppression.

Fertility and Reproductive Outcomes: Fertility-related research remains notably deficient. Emerging single-cell transcriptomic and proteomic analyses reveal disruptions in oocyte maturation pathways linked to oxidative stress and abnormal molecular regulation, correlating with reduced reproductive outcomes in patients with ovarian endometriosis (93). While these data highlight potential molecular pathways affecting ovarian function, translation into clinical practice, such as methods to restore typical oocyte function, remains largely unaddressed. Equally puzzling is why some endometriosis patients maintain robust fertility, whereas others encounter severe, treatment-refractory infertility.

Limitations of Current Hormonal Therapies: Management of endometriosis remains predominantly reliant on broad hormonal suppression, posing significant drawbacks for patients with contraindications or fertility goals. Despite preclinical promise, therapies targeting local estrogen biosynthesis, inflammatory signaling pathways, or dysregulated neuroimmune interactions remain limited in their clinical adoption and validation (94). Moreover, no consensus exists for targeted therapies aimed at local estrogen synthesis, inflammatory pathways, or dysregulated neuroimmune mechanisms without broad hormonal suppression. Novel interventions (for example, lncRNA or circRNA modulators and agents targeting stem-like cells) show promise in preclinical investigations but lack rigorous testing in phase I/II clinical trials (87, 90-92, 94).

DISCUSSION

Endometriosis displays complex cancer-mimicking characteristics that complicate biomarker development and clinical translation (7, 81, 91). Recent proteomic studies identified a promising 10-protein plasma panel achieving high diagnostic accuracy (AUC 0.997), yet its performance varies considerably across disease stages (95). Similarly, saliva-based miRNA signatures combined with artificial intelligence (AI) algorithms achieved sensitivities of 96–97% and specificities up to 95–100% (96, 97). Although these noninvasive tools are promising, false-negative results remain a concern, potentially extending diagnostic delays. Thus, balancing assay accuracy against minimally invasive surgical interventions remains critical. Comparative studies quantifying risks associated with false-negative diagnoses versus surgical morbidity are necessary to inform optimal patient management strategies (10). A fundamental barrier remains the lack of systematic preclinical and early-phase validation frameworks connecting bench research directly to clinical practice. Despite identifying numerous molecular candidates, such as dysregulated noncoding RNAs, epigenetic alterations, and immune checkpoint dysregulation, few have successfully navigated rigorous, phased evaluations in clearly characterized disease models (89). Biomarkers derived from proteomic or metabolomic platforms similarly require validation through large-scale confirmatory studies, which remain insufficient (90). Consequently, invasive diagnostic procedures, broad hormonal suppression, and repeated surgical interventions persist as the predominant standards of care (98). Although endometriosis predominantly remains a benign condition with cancer-mimicking features, a small but clinically important proportion can undergo genuine malignant transformation, particularly to EAOC. Recent studies have elucidated distinct EAOC clinical entities, notably distinguishing between endometriosis-correlated ovarian carcinoma, characterized by transitional lesions such as atypical endometriosis or borderline tumors, and endometriosis-incidental ovarian carcinoma, in which benign endometriosis occurs independently alongside ovarian cancer. Patients with endometriosis-correlated ovarian carcinoma tend to present at younger ages, earlier disease stages, and with different histopathological subtypes compared to ovarian cancers without associated endometriosis, underscoring critical prognostic and therapeutic differences (6). At a molecular level, the transition from benign ovarian endometriosis to carcinoma is associated with specific miRNA profiles, with recent analyses identifying miRNAs, such as hsa-miR-200a-3p, hsa-miR-141-3p, hsa-miR-183-5p, and hsa-miR-10a-5p, that are significantly upregulated during malignant transformation. These miRNA biomarkers offer promising diagnostic potential for the early identification of patients at elevated risk of progression to EAOC but they still need external clinical validation (99). Furthermore, comprehensive molecular and clinical data reinforce the need for individualized management strategies, emphasizing precise molecular diagnostics and targeted therapeutic approaches to optimize outcomes in ovarian cancer management (100). To address these shortcomings, we propose adopting a structured translational approach whereby new hypotheses undergo systematic validation in robust preclinical models before advancing to carefully staged clinical trials within rigorously stratified patient populations (101). Such an approach ensures promising molecular or immunological candidates first undergo Phase 0 trials to determine safety and biological plausibility prior to progressing to larger-scale Phase II/III evaluations. Aromatase inhibitors exemplify how structured, small-scale experimental validations can translate into targeted, non-hormonal therapeutic options (94). Employing this structured pipeline facilitates efficient conversion of laboratory discoveries into clinically applicable tools. Structured translational research also promotes refined clinical phenotyping. By stratifying endometriosis into distinct clinical subtypes (e.g., deep infiltrating, peritoneal, ovarian), novel therapies—such as immune checkpoint modulators, anti-inflammatory compounds, and epigenetic drugs—can be more precisely matched to patient subgroups most likely to respond. This targeted approach reduces reliance on empirical treatment strategies (11). Early-phase models further help define relevant clinical endpoints, such as pain alleviation, fertility restoration, and lesion regression, while incorporating advanced imaging, immunological profiling, and biomarker assessments to measure therapeutic outcomes dynamically. An emerging yet underappreciated concern involves reliance on large-scale data analytics and AI-driven methodologies for identifying molecular signatures and disease subtypes. Without robust, patient-centered translational frameworks, indiscriminate use of AI risks embedding pre-existing biases, amplifying health inequalities, and generating outcomes that neither address patient-specific clinical needs nor tangibly improve clinical care (20, 102). AI models developed on incomplete or biased datasets may further exacerbate misdiagnosis or inappropriate therapeutic decisions. To mitigate these risks, AI applications should undergo transparent, phase-appropriate clinical validation, clearly defined endpoints, and equity-focused performance assessments. Such rigor prevents the pitfalls associated with opaque algorithmic ("black-box") decision-making. Similarly, advanced imaging and machine-learning technologies must follow carefully structured validation pathways prioritizing high-quality data, equitable patient access, and continual monitoring. These measures ensure AI-enhanced strategies meaningfully advance critical clinical outcomes such as pain relief and fertility preservation, thereby safeguarding both scientific integrity and personalized patient care. Ultimately, endometriosis represents a multifaceted, systemic disorder with numerous malignant-like features (11). Establishing a translational roadmap grounded in refined phenotyping, phase-focused validation, and methodical clinical trials is vital. By instituting a well-defined pipeline, clinicians and researchers can move beyond traditional hormonal treatments, ultimately delivering targeted, effective interventions and significantly improving quality of life for women who currently endure the substantial burdens of endometriosis.

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COMPLIANCE WITH ETHICAL STANDARDS

Fundings

No funding was utilized for this study as it comprised observational research incorporating routine clinical practices.

Conflict of interests

The authors declare that there are no conflicts of interest associated with this publication.

Availability of data and materials

The data supporting the findings of this study are available upon reasonable request to the corresponding author.

Authors' contributions

CM: Conceptualization, Methodology, Formal analysis, Writing – Original Draft, Supervision, Project administration. AV: Conceptualization, Investigation, Resources, Writing – Review & Editing, Supervision. FDC: Formal analysis, Visualization, Writing – Original Draft. GM: Validation, Formal analysis, Data Curation. SEM: Investigation, Data Curation, Writing – Original Draft. LA: Formal analysis, Investigation, Validation. AE: Investigation, Resources, Validation, Writing – Review & Editing. AG: Supervision, Project administration, Funding acquisition, Writing – Review & Editing.

Ethical approval

This research adhered to the ethical standards of the World Medical Association's Declaration of Helsinki and complies with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, including the inclusion of diverse human populations in terms of sex, age, and ethnicity.

Human studies and subjects

N/A.

Animal studies

N/A.

Publications ethics

The publication ethics followed by this study align with those outlined by the International Committee of Medical Journal Editors (ICMJE), regarding publishing and editorial issues in medical journals.

Plagiarism

The article provides a comprehensive review of the latest studies in the field, with accurate citations.

Data falsification and fabrication

The writing and contents of the article are entirely original and were developed entirely by the authors.

Abbreviations

AI: Artificial Intelligence
AKT: Protein Kinase B (also referred to as "PKB")
AXL: AXL Receptor Tyrosine Kinase
Bcl-2: B-cell lymphoma 2
CA-125: Cancer Antigen 125
CA-19.9: Cancer Antigen 19.9
CD74: Cluster of Differentiation 74
circRNA: Circular RNA
COX-2: Cyclooxygenase-2
CT: Computed Tomography
CTLA-4: Cytotoxic T-lymphocyte-Associated Protein 4
EAOC: Endometriosis-Associated Ovarian Cancer
EMT: Epithelial–Mesenchymal Transition
ENPP3: Ectonucleotide Pyrophosphatase/Phosphodiesterase 3
ERβ: Estrogen Receptor Beta (also written as ESR2)
ERK: Extracellular Signal-Regulated Kinase
FGFR2: Fibroblast Growth Factor Receptor 2
Gal-9: Galectin-9
GC–MS: Gas Chromatography–Mass Spectrometry
GM-CSF: Granulocyte Macrophage Colony-Stimulating Factor
HDAC: Histone Deacetylase
HIF-1α: Hypoxia-Inducible Factor 1-Alpha
HOXA-AS2: HOXA Cluster Antisense RNA 2
HOTAIR: HOX Transcript Antisense RNA
IGF2BP2: Insulin-like Growth Factor 2 mRNA-Binding Protein 2
IKKβ: IκB Kinase Beta
IL-1β: Interleukin 1 Beta
IL-6: Interleukin 6
IL-8: Interleukin 8
IL6ST (gp130): Interleukin 6 Signal Transducer (glycoprotein 130)
JAK: Janus Kinase
JNK: c-Jun N-terminal Kinase
lncRNA: Long Noncoding RNA
MAPK: Mitogen-Activated Protein Kinase
MCP-1: Monocyte Chemoattractant Protein 1 (also known as CCL2)
MDSCs: Myeloid-Derived Suppressor Cells
MIF: Macrophage Migration Inhibitory Factor
miRNA: MicroRNA

MRI: Magnetic Resonance Imaging
mTOR: Mechanistic Target of Rapamycin
MyD88: Myeloid Differentiation Primary Response 88
N-cadherin: Neural Cadherin
NCOA-1: Nuclear Receptor Coactivator 1
NF-κB: Nuclear Factor kappa B
p38: p38 Mitogen-Activated Protein Kinase
pAKT: Phosphorylated AKT
PD-1: Programmed Cell Death Protein 1
PD-L1: Programmed Death-Ligand 1
PET: Positron Emission Tomography
PI3K: Phosphatidylinositol 3-Kinase
PRRG4: Proline-Rich Gla (γ-carboxyglutamic acid) Protein 4
PTEN: Phosphatase and Tensin Homolog
Raf: Rapidly Accelerated Fibrosarcoma (proto-oncogene in the MAPK pathway)
RANTES: Regulated upon Activation, Normal T Cell Expressed and Secreted (also known as CCL5)
RASSF1A: Ras Association Domain Family Member 1
SHC1: SHC Adaptor Protein 1 (Src Homology 2 domain-containing)
SFRP2: Secreted Frizzled-Related Protein 2
SOD2: Superoxide Dismutase 2
STAT: Signal Transducer and Activator of Transcription
TGFβ: Transforming Growth Factor Beta
TIM-3: T-cell immunoglobulin and mucin-domain containing-3
TLR4: Toll-Like Receptor 4
TNFα: Tumor Necrosis Factor Alpha
TSLP: Thymic Stromal Lymphopoietin
VEGF: Vascular Endothelial Growth Factor
VEGFR: Vascular Endothelial Growth Factor Receptor
WEE1: WEE1 G2 Checkpoint Kinase
Wnt: Wingless/Integrated
4EBP1: Eukaryotic Translation Initiation Factor 4E-Binding Protein 1

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