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PREVALENCE, ULTRASOUND CHARACTERIZATION, AND ONCOLOGIC DIFFERENTIAL DIAGNOSIS OF ENDOMETRIOSIS IN POSTMENOPAUSAL WOMEN UNDERGOING ROUTINE GYNECOLOGICAL EXAMINATION

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Questa **tesi** è dedicata

a **Chiara**, amore della mia vita, fonte di luce inesauribile, futura mamma della nostra piccola **Livia**.

Ai nonni **Gabriele** e **Michele**, che continuano a vivere in me,

a **papà** e **mamma**, alle **nonne Adelina** e **Michela**, e a tutta la famiglia,

per l'amore e il supporto senza fine.

Agli **amici** di sempre e a quelli incontrati lungo il cammino, che rendono il quotidiano più leggero e offrono sostegno nei momenti che contano, con particolare riferimento a **Umberto**, compagno di strada in molte tappe di questo percorso.

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1. INTRODUCTION

Endometriosis is a benign, chronic inflammatory gynecological disorder characterized by the presence of endometrial-like tissue located outside the uterine cavity. This condition affects a considerable proportion of women of reproductive age, with an estimated prevalence ranging between 5% and 10% [1]. Endometriotic lesions vary according to anatomical location and morphology and may be classified into superficial peritoneal endometriosis, deep infiltrating endometriosis, and ovarian endometriomas, which correspond to cystic lesions of endometriotic origin located within the ovaries.

The clinical presentation of endometriosis is highly heterogeneous. While some women remain asymptomatic, others may experience significant symptoms, including severe menstrual pain (dysmenorrhea), chronic pelvic pain, dyspareunia, and pain or difficulty with urination (dysuria) or defecation (dischezia), along with additional gastrointestinal disturbances. These manifestations can profoundly impair quality of life and exert a marked socioeconomic impact, comparable to other chronic diseases such as type II diabetes and rheumatic disorders [2, 3].

Endometriosis may also negatively affect fertility in approximately 35–50% of affected women. Multiple mechanisms have been implicated, including pelvic adhesions, tubal obstruction, alterations in the peritoneal microenvironment, hormonal imbalance, and impaired oocyte quality [4].

Beyond the physical implications, endometriosis carries psychological consequences, as the burden of chronic pain and potential infertility may predispose patients to the development of anxiety and depression, further worsening emotional distress and overall quality of life [5].

Despite its high prevalence, endometriosis is frequently diagnosed after a substantial delay. In Italy, an average of 7 to 10 years elapse between the onset of symptoms and clinical diagnosis [6]. This delay is even more pronounced in younger patients, particularly adolescents, since initial symptoms such as dysmenorrhea are often perceived as physiological or dismissed, hindering early recognition.

Diagnostic challenges are further compounded by the absence of specific serum biomarkers and by limited awareness of the disease among healthcare professionals and the general population.

Therapeutic options depend on disease severity and include both medical and surgical approaches. Medical treatments encompass analgesic regimens for pain control and hormonal therapies. Surgical intervention is usually reserved for more severe cases in which symptoms are refractory to medical therapy or in the presence of complications, such as bowel or ureteral obstruction. Moreover, surgery may be considered in women with infertility, with the aim of excising endometriotic lesions to improve conception rates [7].

In conclusion, endometriosis is a benign yet complex gynecological condition requiring early diagnosis and a multidisciplinary treatment strategy. An integrated approach is essential not only for pain management and preservation of fertility, but also for addressing sexual dysfunction arising from chronic pain, while mitigating the psychological and social burden associated with the disease.

2. PATHOPHYSIOLOGY

2.1 Pathogenetic Theories of Endometriosis

The pathophysiology of endometriosis is complex and multifactorial, involving the interaction of anatomical, hormonal, immunological, inflammatory, estrogenic, genetic, epigenetic, and environmental factors. The clinical and morphological heterogeneity of its main manifestations (peritoneal, ovarian, and deep endometriosis) suggests distinct pathogenetic pathways [8]. A widely accepted hypothesis proposes that endometriosis may initially represent a transient phenomenon, potentially occurring in many women during menstruation, but evolving into a chronic symptomatic condition only in a predisposed subgroup [9].

The retrograde menstruation theory proposed by Sampson in 1927 remains the most established explanation for the pathogenesis of endometriosis. According to this hypothesis, endometrial tissue

refluxes through the fallopian tubes during menstruation, reaching the peritoneal cavity, where it may implant and develop lesions through proliferative and angiogenic processes [10]. The presence of menstrual blood in the peritoneal fluid has been documented in up to 90% of women with patent tubes, and the demonstrated viability of retrogradely shed endometrial cells further supports their pathogenic potential. Moreover, the predominant anatomical distribution of lesions, particularly in the left hemipelvis and along the right hemidiaphragm, appears consistent with the counterclockwise flow of peritoneal fluid. However, this theory alone does not explain all clinical manifestations, such as cases in the absence of menstruation (before menarche, after menopause, or in patients with Rokitansky syndrome) or extrapelvic presentations. In addition, significant differences between eutopic and ectopic endometrium support the concept that, in affected women, the endometrium itself may present intrinsic biological features that promote ectopic colonization [11, 12].

The metastatic theory extends this concept, suggesting hematogenous or lymphatic dissemination of endometrial tissue to distant sites such as the thoracic cavity, thereby accounting for extrapelvic lesions [12]. Iatrogenic implantation following surgical procedures (e.g., abdominal wall endometriosis after cesarean section) also falls within this transplantation-based mechanism.

In situ origin theories propose that endometriosis arises from local transformation of cells already present at ectopic sites. In this context, the embryonic rest theory suggests that ectopic Müllerian cells, derived from abnormal migration during embryonic development, may differentiate into endometrial tissue under hormonal stimulation, thus explaining lesions in individuals without menstruation, in the presence of uterovaginal agenesis, or, rarely, in males [8]. The coelomic metaplasia theory, formulated by Waldeyer in 1870, posits that coelomic epithelium—origin of both the peritoneum and the endometrium—may transform into endometrial tissue in response to inflammatory, hormonal, or biochemical stimuli. Closely related is the induction theory, which proposes that endogenous or immune factors may trigger endometrial differentiation in undifferentiated cells [11, 13].

These theories effectively explain cases in which endometriosis develops without contribution from eutopic endometrium. However, they do not fully justify the preferential pelvic localization of lesions, the anecdotal incidence in males, or the lack of correlation with age. Moreover, although early observations suggested a higher prevalence of endometriosis in association with non-obstructive Müllerian anomalies, later evidence indicates a stronger association with obstructive anomalies [14, 15].

2.2 Role of the Immune System and Inflammation

Peritoneal fluid, derived from peritoneal and ovarian exudation, creates a microenvironment rich in various cellular components, including immune cells, endometrial cells, and erythrocytes. These cells secrete growth factors, angiogenic molecules, and cytokines that may influence biological processes within the abdominal cavity. Studies have shown that endometrial cells present within the peritoneal cavity differ from eutopic cells residing in the uterine endometrium, due to distinct environmental conditions between peritoneal fluid and the bloodstream [16].

In the presence of endometriosis, ectopic endometrial tissue triggers an inflammatory response that would normally remove abnormal cells and tissue. However, in women with endometriosis, the immune system appears unable to effectively eliminate ectopic tissue, likely due to heavier and prolonged menstrual flow that exceeds the immune system's clearance capacity within the abdominal cavity [17, 18]. This phenomenon may be related to the release of larger volumes of endometrial fragments into the abdominal cavity during the menstrual cycle, overwhelming immune clearance mechanisms [19, 20].

Ectopic endometrial cells may also be more resistant to the cytotoxic activity of immune cells, particularly macrophages and natural killer (NK) cells, which normally destroy damaged or foreign cells. Indeed, NK cell cytotoxicity against endometrial cells appears reduced, a finding associated with disease progression [21, 22]. Ectopic endometrial cells seem to evade immune destruction through mechanisms such as overexpression of the soluble intercellular adhesion molecule sICAM-

1, which interferes with leukocyte recognition and activation. Specifically, this molecule prevents the binding of other receptors that would otherwise activate immune cells [23].

Inflammation in endometriosis is further amplified by the production of cytokines, including cyclooxygenase-2 (COX-2) and various interleukins, and by oxidative stress, which alters intracellular signaling pathways such as mitogen-activated protein kinase (MAPK) cascades. These alterations heighten inflammation and activate immune cells, leading to an exaggerated inflammatory response that promotes the release of growth factors and the development of pain hypersensitivity. Additionally, dysregulation of apoptotic mechanisms contributes to the inability of the immune system to remove ectopic tissue [24, 25].

Persistent ectopic endometrial tissue within the abdominal cavity induces chronic inflammation and sustained macrophage activation. Although macrophage numbers are increased in women with endometriosis, their ability to effectively remove abnormal tissue is reduced [26]. Protection of macrophages from apoptosis, mediated by overexpression of the Bcl-2 protein, prevents their elimination once their role is complete [27]. Moreover, an imbalance between M1 and M2 macrophage subsets has been identified, with M2 macrophages predominating within endometriotic lesions. While M1 macrophages are responsible for pathogen elimination and inflammation promotion, M2 macrophages participate in tissue repair and angiogenesis, favoring endometriotic lesion survival [24, 28].

In women with endometriosis, eutopic endometrial tissue exhibits reduced secretion of pro-inflammatory cytokines that normally activate M1 macrophages, whereas M2 macrophages predominate in ectopic endometrium [27, 29]. This cytokine and macrophage imbalance supports ectopic tissue survival and growth, peritoneal mesothelial metaplasia, and extracellular matrix remodeling. Altered immune responses also promote lesion survival and implantation by stimulating angiogenesis and cellular proliferation, particularly through factors such as IL-6, IL-8, and TNF-α [30, 31].

These immunological abnormalities appear to impair the ability of the immune system to recognize and eliminate ectopic endometrial tissue. Such immune dysfunctions may therefore represent either a cause or consequence of endometriosis, but are now recognized to play a central role in disease pathogenesis.

2.3 Hormonal Microenvironment

Local estrogen production plays a central role in the pathogenesis of endometriosis and other benign and malignant conditions of the female reproductive tract. Aromatase P450 (CYP19A1), the key enzyme responsible for the conversion of androgens to estrogens, is normally expressed in tissues such as the ovaries and adipose tissue, but not in healthy endometrium [32, 33]. In women with endometriosis, however, ectopic expression of aromatase has been demonstrated in both endometriotic lesions and eutopic endometrium [34], leading to increased local synthesis of 17β-estradiol (E2), the primary estrogen implicated in disease-related growth, inflammation, and pain.

This E2 production is further supported by the steroidogenic acute regulatory protein (StAR), which facilitates mitochondrial cholesterol transport, the first step in steroidogenesis. Both enzymes are overexpressed in endometriotic tissue and absent in normal endometrium [35].

Another relevant pathogenetic mechanism is reduced activity of 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2), which normally inactivates E2 by converting it into estrone, a less potent estrogen. Deficiency of 17β-HSD2 thus contributes to elevated local E2 levels [36], confirming a heightened estrogenic environment in affected patients, as also demonstrated by increased estrogen concentrations in menstrual effluent compared with healthy controls [37].

Excessive E2 production establishes a positive feedback mechanism mediated by cyclooxygenase-2 (COX-2), which enhances prostaglandin E2 (PGE2) synthesis, further stimulating aromatase. This mechanism is also supported by the tissue injury and repair (TIAR) process, induced by microtrauma to the basal endometrial layer. This layer, rich in stem cells, may promote chronic inflammation and

local estrogen synthesis under peritoneal ectopic conditions, fostering proliferation and invasiveness of endometriotic tissue [8].

This abnormal estrogenic environment also activates resident peritoneal macrophages, inducing secretion of pro-inflammatory cytokines such as TNF-α and IL-1β, which stimulate NF-κB signaling and contribute to an inflammatory microenvironment favorable to ectopic tissue implantation and growth [38]. In addition, crucial factors such as vascular endothelial growth factor (VEGF), cell-cycle regulatory molecules, and the anti-apoptotic gene Bcl-2 support cellular survival and reduce apoptosis in ectopic endometrial cells.

Parallel to this, progesterone resistance within endometriotic lesions prevents antagonism of estrogenic stimulation, further worsening hormonal imbalance. This resistance is partially due to epigenetic mechanisms, including hypermethylation of progesterone receptor genes, histone acetylation, and differential expression of microRNAs, all of which are more prevalent in endometriotic tissue than in eutopic endometrium [39].

3. EPIDEMIOLOGY AND RISK FACTORS

3.1 Epidemiology

According to the main reviews of the scientific literature, endometriosis affects a substantial proportion of women of reproductive age, estimated at approximately 5–10%, although the reported data show considerable heterogeneity. This variability can be attributed to multiple factors, including the temporal evolution of the disease, differences among the populations analyzed, the diagnostic criteria adopted (which may be based on clinical assessment or histological confirmation), the level of diagnostic awareness, the selection of patients undergoing surgical procedures, the potential inclusion of adenomyosis cases, and the different techniques used for pelvic exploration [1].

The incidence of endometriosis increases to 50–80% among women with pelvic pain and to approximately 50% among women with infertility. Globally, it is estimated that more than 176

million women are affected by this condition. Prevalence is particularly high in patients with chronic pelvic pain, but the disease is also frequently identified among asymptomatic women, in whom endometriosis may be detected in 45–50% of cases, especially when microscopic histological diagnosis is taken into account.

It is important to emphasize that not all suspicious lesions observed at the peritoneal level correspond to endometriosis, as some may represent normal anatomical variants. In this context, assessment of clinical symptomatology plays a pivotal role and may, in some cases, be more indicative of disease than the mere presence of visible lesions. Conversely, the absence of macroscopic findings does not exclude the diagnosis, as cases of occult endometriosis have been described in which the disease was identified exclusively through random peritoneal biopsies. Consequently, relying solely on a surgical approach for diagnosis may result in delayed initiation of treatment for a complex and multifactorial condition such as endometriosis [1].

3.2 Risk Factors

Numerous epidemiological studies have sought to identify risk factors that increase susceptibility to endometriosis, although in many cases the observed associations do not necessarily imply a causal relationship. Some factors appear to exert a direct impact on endometriosis risk, whereas others may act as contributing factors or influence the likelihood of diagnosis [40].

A family history of endometriosis in first-degree relatives represents one of the most consistently established risk factors. Women with an affected sister or mother have up to a nine-fold higher risk compared with the general population [41]. Familial aggregation may reflect both a genetic predisposition, supported by genome-wide association studies identifying multiple loci involved in hormonal and immune regulation [42], and a potential surveillance bias, as awareness of a familial diagnosis increases the likelihood of specialist consultation and diagnostic investigation [43].

Early menarche, short menstrual cycles, and heavy menstrual bleeding have been associated with an increased risk of endometriosis [44]. These factors suggest greater exposure to retrograde menstrual

flow, supporting the retrograde menstruation theory as a pathogenetic mechanism [45]. In particular, a higher number of ovulatory cycles not interrupted by pregnancy or hormonal contraceptive use may favor the implantation of ectopic endometrial cells.

Nulliparity has been frequently identified as a risk factor. The proposed mechanism relates to the absence of prolonged periods of physiological amenorrhea, such as those induced by pregnancy, which would otherwise reduce exposure to menstrual flow. Furthermore, pregnancy is characterized by a progestin-dominant endocrine environment that appears to exert an inhibitory effect on endometriotic lesion activity [46].

Current use of combined oral contraceptive (COC) appears to be associated with a reduced risk of endometriosis, owing to their ability to suppress ovulation and decrease menstrual flow [47].

A low body mass index has been inversely correlated with endometriosis risk [48]. Women with a lower body mass index appear to have a higher risk, although this association may partly reflect diagnostic bias related to a greater likelihood of undergoing investigations for infertility. Other studies have demonstrated a correlation with body size during childhood and adolescence [49], suggesting that constitutional factors may influence disease development.

In some studies, higher educational attainment and socioeconomic status have been associated with a greater prevalence of diagnosis [50]. This relationship may be explained by increased symptom awareness and improved access to healthcare services. Prolonged night-shift work exceeding five years has also been associated with a slightly increased risk among women with infertility [51], possibly through disruption of circadian rhythms and hormonal balance.

Regular physical activity may exert a protective effect by reducing circulating estrogen levels, increasing Sex Hormone-Binding Globulin (SHBG), and improving insulin sensitivity [52]. However, findings remain inconsistent, and some studies have failed to confirm a significant association [53]. Alcohol consumption has been correlated with an increased risk in a dose-dependent manner [54], whereas no consistent associations have been identified with cigarette smoking [55] or caffeine intake [56].

The role of diet has attracted increasing interest, as dietary patterns may influence inflammatory and hormonal pathways relevant to endometriosis pathophysiology [45]. Some evidence suggests a potential protective effect of diets rich in fruits, vegetables, and omega-3 fatty acids; however, the available data remain limited and partially contradictory [54].

The hypothesis that environmental pollutants such as dioxins, phthalates, and bisphenol A may increase endometriosis risk is based on their capacity to interfere with endocrine and immune regulation. Nevertheless, current evidence remains insufficient to establish a definitive causal relationship [57].

Women with endometriosis frequently report gastrointestinal symptoms and exhibit a higher incidence of chronic inflammatory bowel diseases, even years after diagnosis [58]. A shared pathogenetic mechanism has been hypothesized, mediated by immune dysfunction and alterations in intestinal barrier integrity. Endometriosis is also associated with an increased prevalence of autoimmune diseases, including thyroiditis, rheumatoid arthritis, psoriasis, allergies, and asthma [59, 60], suggesting a potential autoimmune component in its etiopathogenesis, although it remains unclear whether such immune dysfunction represents a cause or a consequence of the disease. Finally, recent studies have proposed an association with an increased risk of cardiovascular disease, an issue that warrants further investigation [61].

4. ENDOMETRIOSIS-RELATED PAIN

Endometriosis is characterized by a heterogeneous clinical presentation, with symptoms varying according to lesion location. Pain represents the most common and disabling symptom, although it is not always proportional to the extent of disease. It may be nociceptive, neuropathic, or mixed in nature, and may present as chronic pain or occur in relation to specific circumstances, such as sexual

intercourse (dyspareunia), defecation (dyschezia), urination (dysuria), or menstruation (dysmenorrhea).

Pain in endometriosis arises from a complex interplay of biological processes, in which inflammation, peripheral and central nervous system alterations, and immune–neural interactions play a pivotal role (**Figure 1**) [62]. Pain perception is not merely the result of the presence of endometriotic tissue, but is also modulated by psychological factors, physical stress, and hormonal fluctuations. In this context, chronic pelvic pain may lead to significant emotional, behavioral, and sexual consequences, which in turn can further amplify the pain experience [63].

One of the key mechanisms involved is local inflammation. Endometriotic lesions harbor immune cells such as macrophages and NK cells, which produce high levels of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α. These mediators not only promote endometriotic cell proliferation but also stimulate nerve fiber growth, establishing a self-sustaining neuroinflammatory loop. The secretion of neurotrophic factors, particularly nerve growth factor (NGF), further enhances nerve sprouting and increases afferent fiber sensitivity. Within this microenvironment, the close spatial relationship between newly formed vessels, nerve fibers, and immune cells fosters a tight interaction between neuroangiogenesis and inflammation, consolidating a pathological framework that promotes pain chronicization [64].

Endometriotic lesions exhibit dense sensory and sympathetic innervation, mainly composed of small-diameter unmyelinated fibers (C fibers) that convey pain-related neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) [65]. In deep endometriosis nodules, these fibers penetrate deeply into fibrotic tissue and extend to the peripheral regions of the lesions, directly contributing to pain perception.

Persistent stimulation of peripheral nociceptors by local inflammation and rich innervation leads to peripheral sensitization. Pro-inflammatory mediators such as prostaglandins, TNF-α, and interleukins lower the activation threshold of nerve fibers and enhance nociceptive transmission [66]. Over time,

this state of peripheral hyperexcitability may promote the development of central sensitization, characterized by increased responsiveness of spinal and supraspinal neurons to painful stimuli [67]. Central sensitization accounts for clinical manifestations such as generalized hyperalgesia, defined as an increased pain response to normally nociceptive stimuli, and persistent allodynia, in which pain arises in response to typically non-painful stimuli. It also helps explain the poor correlation between pain severity and disease stage [68].

Functional neuroimaging studies have demonstrated alterations in brain connectivity and plasticity of pain pathways in patients with endometriosis, suggesting involvement of central neural circuits in chronic pain perception [69]. This mechanism also contributes to the frequent association between endometriosis-related pain and other chronic pain syndromes, such as chronic pelvic pain syndrome, fibromyalgia, and irritable bowel syndrome, all characterized by dysfunctions in descending pain modulation and the autonomic nervous system.

Understanding these interconnected processes linking inflammation, innervation, and central sensitization opens new therapeutic perspectives. Beyond hormonal suppression and surgical interventions, management of chronic pain may require multimodal approaches, including neuromodulatory drugs, pelvic floor physiotherapy, and psychological interventions aimed at reducing neuronal hyperexcitability. Targeting neurotrophic mediators and modulating the local immune response represent promising strategies to control pain and limit disease progression [64].

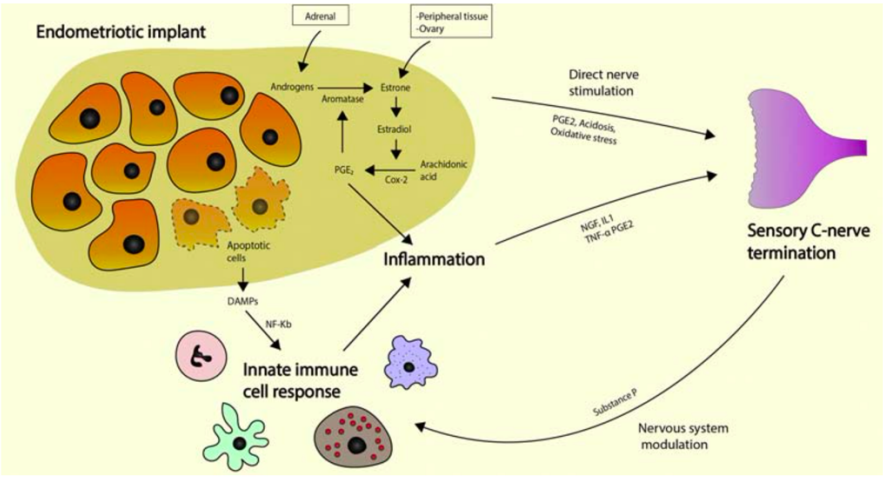

Figure 1. Schematic representation of the neuro-inflammatory and hormonal mechanisms underlying endometriosis-associated pain. Ectopic endometrial implants locally produce estrogens via aromatase activity, sustaining inflammation through prostaglandin (PGE_2) and cytokine signaling. Cellular stress and apoptosis release damage-associated molecular patterns (DAMPs), activating innate immune responses and amplifying inflammatory cascades (NF-κB pathway). Inflammatory mediators and neurotrophic factors (e.g., NGF, IL-1, TNF-α) promote peripheral nerve sensitization and direct stimulation of sensory C-fiber nerve endings, leading to peripheral and central sensitization and chronic pelvic pain.

5. CLASSIFICATIONS

Given the variability of endometriosis in terms of extent, severity, and anatomical location, several classification systems have been developed over time.

Currently, the most widely used classification systems include r-ASRM, Enzian, AAGL, and EFI. However, none of them is free from criticism, as they do not consistently reflect correlations with symptoms, do not reliably predict prognosis, and do not effectively guide therapeutic decision-making, particularly with regard to pelvic pain and infertility.

5.1 r-ASRM Classification (Revised American Society for Reproductive Medicine)

The r-ASRM classification is the most widely used system and was introduced in 1997. It is based on a scoring system assigned to lesions visualized during laparoscopy, according to the size of endometriotic implants, the presence of ovarian cysts and adhesions, and the degree of obliteration of the pouch of Douglas.

The total score determines four stages of disease [70]:

-Stage I – Minimal: few superficial lesions, absence of scar tissue.

-Stage II – Mild: more numerous and slightly deeper implants.

-Stage III – Moderate: multiple implants, small ovarian cysts, and adhesions.

-Stage IV – Severe: deep lesions, large endometriomas, extensive adhesions, and involvement of adjacent organs.

This system is simple to apply but does not assess involvement of deep retroperitoneal structures, limiting its effectiveness in describing deep endometriosis. For this reason, subsequent classification systems were developed.

5.2 Enzian Classification

The Enzian classification (**Figure 2**) provides a detailed description of deep endometriosis by dividing the pelvis into three anatomical compartments:

-Compartment A: vagina and rectovaginal septum

-Compartment B: uterosacral ligaments and pelvic walls

-Compartment C: sigmoid colon and rectum

Additional specific codes are used to indicate lesions located in extra-compartmental sites. In the updated classification, invasion of pelvic or extrapelvic organs is indicated by the prefix “F”, derived from the English terms “far” or “foreign”, referring to distant or external structures. The associated abbreviations precisely identify the sites involved:

-FA: adenomyosis

-FB: bladder involvement

-FU: ureteral involvement

-FI: intestinal involvement above the sigmoid colon

-FO: involvement of other anatomical structures, such as the abdominal wall

Several studies have demonstrated a good correlation between the Enzian classification and parameters such as surgical complexity, operative time, and symptom severity. Despite representing a more detailed classification attempt, the Enzian system has not achieved widespread adoption within the scientific community [70]. One of its main limitations lies in the anatomical subdivision

into compartments A, B, and C, which do not correspond to clearly identifiable physical boundaries. This makes precise lesion mapping challenging, particularly at transition points between compartments. Furthermore, the complexity of the nomenclature limits patient comprehension and, as with other classification systems, its association with clinically relevant symptoms such as pain and infertility remains weak.

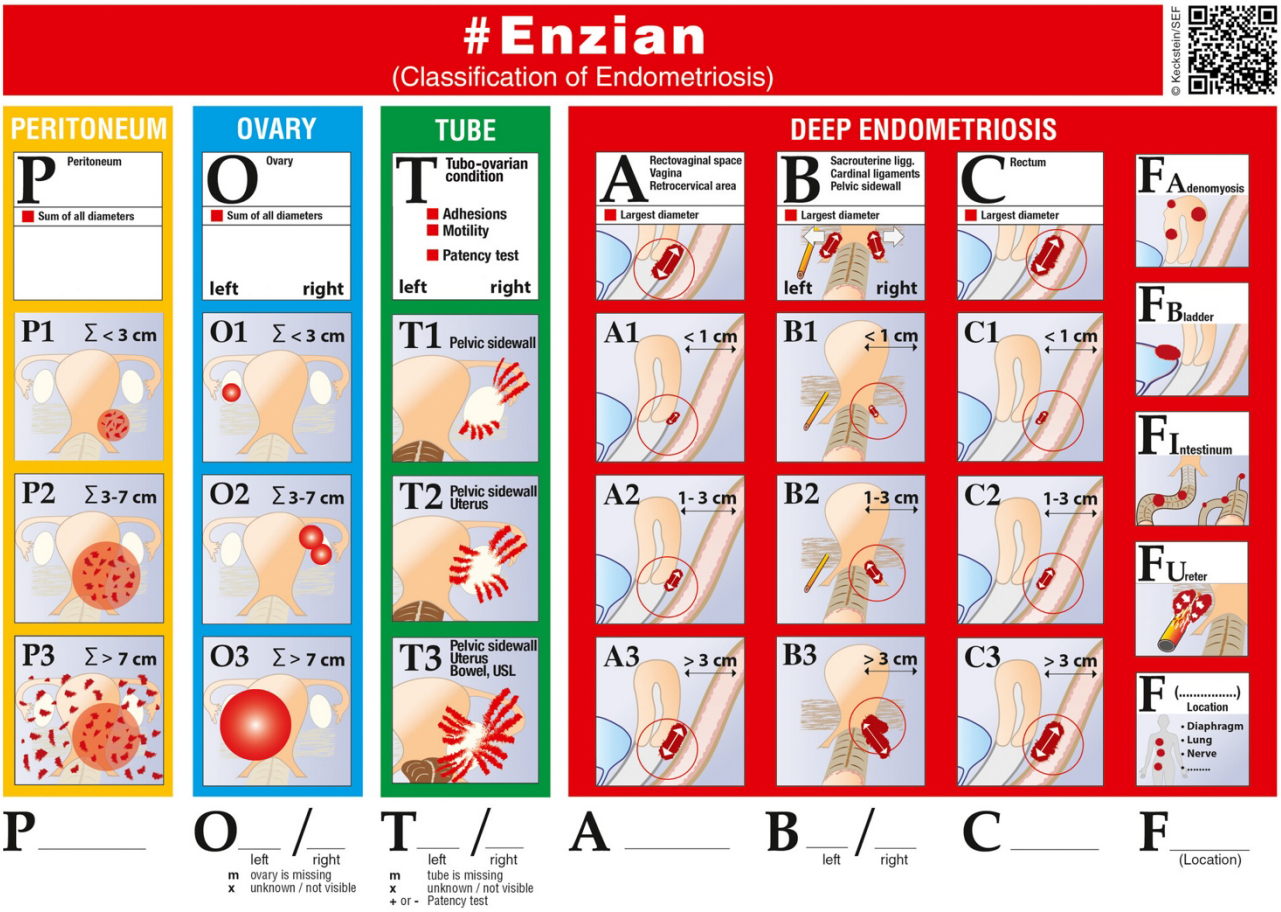

Figure 2. Enzian classification of endometriosis.

Schematic representation of the Enzian classification system for the anatomical description and staging of endometriosis. The system categorizes lesions according to their topographic distribution and maximal lesion diameter [70].

5.3 AAGL Classification 2021

The AAGL (American Association of Gynecologic Laparoscopists) classification is designed to provide a detailed assessment of endometriosis extent and the degree of pelvic organ involvement. It is based on assigning a score to each anatomical site, taking into account lesion size and depth, anatomical location, and the presence of complications.

Several anatomical areas are evaluated, including the peritoneum, vagina, ovaries, fallopian tubes, ureters, rectovaginal septum, bladder, intestine (rectum, sigmoid colon, small bowel, cecum), and appendix. The score varies according to:

-Lesion size: <3 cm or ≥3 cm.

-Depth of infiltration: superficial or deep.

-Functional involvement: organ immobility, obstruction, hydroureter.

For example, superficial peritoneal lesions are assigned low scores, whereas deep or large lesions receive higher scores. Involvement of organs such as the ureters, bladder, or intestine results in even higher scores due to greater anatomical complexity. Involvement of the rectovaginal septum, fallopian tubes, or appendix is also assigned specific scores, reflecting disease severity [71].

By summing the scores, an overall severity stage is obtained:

-Stage 1 (≤8 points): minimal disease.

-Stage 2 (9–15 points): mild disease.

-Stage 3 (16–21 points): moderate disease.

-Stage 4 (>21 points): severe disease.

5.4 EFI Classification (Endometriosis Fertility Index)

Unlike other systems, the EFI was specifically developed to assess reproductive prognosis in women with endometriosis who desire pregnancy.

This index combines clinical and surgical data:

-patient age

-duration of infertility

-presence or absence of previous pregnancies

-status of the fallopian tubes, ovaries, and residual endometriosis after surgical treatment.

The final score ranges from 0 to 10, with higher values indicating a greater probability of spontaneous conception. EFI is particularly useful in guiding therapeutic decisions (e.g., surgery versus assisted reproductive techniques) in infertile women with endometriosis [72].

Although each classification system offers a different perspective, none alone provides a comprehensive representation of the disease. Integration of these systems, together with correlation with patient-reported symptoms, currently represents the most useful approach for personalized management of endometriosis.

6. DIAGNOSIS

6.1 Anamnesis

Initial evaluation of a patient with suspected endometriosis requires a structured approach, beginning with a thorough medical history. This phase represents a crucial step not only for the collection of relevant clinical information but also for establishing a relationship of trust that facilitates adherence to the diagnostic and therapeutic pathway. Anamnesis focuses on detailed characterization of pain in terms of location, intensity, periodicity, duration, and triggering or relieving factors, in order to guide subsequent investigations. Assessment of pain and its impact on daily life may rely on standardized and validated scales, such as the Visual Analog Scale (VAS), as well as more comprehensive tools, including the Endometriosis Health Profile-30 (EHP-30) questionnaire [73].

Medical history should also include the collection of data regarding systemic comorbidities, previous surgical procedures, oncological history, prior pregnancies, infertility, and reproductive desire. Particular attention should be paid to the presence of suggestive symptoms, such as severe dysmenorrhea, chronic pelvic pain, deep dyspareunia, metrorrhagia, bowel habit alterations

(dyschezia, diarrhea, or cyclical constipation), dysuria, and urinary symptoms related to the menstrual cycle.

6.2 Clinical Examination

Clinical examination in patients with suspected endometriosis should be performed systematically, as it represents a key step in the diagnostic pathway recommended by current guidelines, even though a negative finding does not exclude the disease. Inspection of the posterior vaginal fornix using a speculum may reveal retractions or bluish-black nodules; bimanual palpation allows assessment of uterine and adnexal size and mobility, as well as evaluation of possible alterations involving the vesicouterine space, retrocervical region, uterosacral ligaments, rectovaginal septum, and pouch of Douglas. Digital rectal examination completes the assessment, providing additional information on the rectum, parametrium, and pelvic visceral fascia [74].

Suspicion of parametrial involvement may arise, particularly in experienced hands, from the detection of infiltration at the posterolateral vaginal fornix, frequently associated with induration and pain on palpation during combined vagino-rectal examination [75]. Evaluation of the anterior parametrium and vesicovaginal space is performed by inserting a finger into the anterior fornix while applying gentle suprapubic pressure, whereas assessment of the lateral and posterior parametrium requires placement of one finger in the posterior fornix and another in the rectum. This maneuver allows appraisal of tissue consistency and detection of nodularity or retraction [76].

A recent Italian study demonstrated that physical examination shows good specificity (>80%) for anterior and posterior parametrial infiltration, whereas specificity is lower for lateral involvement; sensitivity, however, remains limited for the anterior and lateral parametrium (≤80%) [77].

These findings indicate that, despite limited sensitivity, physical examination remains a useful tool for orienting diagnostic suspicion, particularly when reduced uterine mobility, palpable nodules, or visible lesions of the posterior fornix are identified.

6.3 Ultrasound Diagnosis

6.3.1 Transvaginal Ultrasound

Transvaginal ultrasound currently represents the first-line non-invasive imaging modality for the evaluation of patients with suspected endometriosis. Endometriosis may present with three main phenotypes: superficial peritoneal implants, ovarian endometriomas, and deep lesions.

This technique has demonstrated high sensitivity and specificity in the detection of ovarian endometriomas and deep endometriosis lesions, as well as in the assessment of pelvic adhesions secondary to the disease. A systematic ultrasound approach for the evaluation of superficial endometriosis has been proposed more recently. However, identification of superficial peritoneal implants generally remains beyond the diagnostic capabilities of ultrasound, due to their small size, variable localization, and lack of sonographically detectable structural alterations.

To standardize ultrasound assessment and improve diagnostic accuracy, the International Deep Endometriosis Analysis (IDEA) group proposed a four-step protocol designed for the ultrasound evaluation of patients with chronic pelvic pain [78].

STEP 1: Assessment of the uterus and adnexa

During transvaginal ultrasound examination, it is essential to assess uterine position (anteverted, retroverted, or axial) and degree of mobility, as reduced or absent mobility may suggest the presence of adhesions. Initial evaluation should focus on identifying sonographic signs of adenomyosis, described according to the Morphological Uterus Sonographic Assessment (MUSA) consensus criteria, as adenomyosis is frequently associated with deep endometriosis [79].

To standardize and improve sonographic reporting of adenomyosis, the MUSA group introduced a set of morphological criteria in 2015, which were subsequently revised in an updated Delphi consensus published in 2022 (**Figure 3**) [80]. In the revised Delphi consensus, experts agreed on seven ultrasound features considered highly indicative of adenomyosis:

-asymmetry of the myometrial walls

-myometrial cysts

-isolated hyperechoic islands

-linear or irregular hyperechoic striations

-heterogeneous myometrial echotexture

-disruption of the junctional zone

-focal or diffuse thickening of the junctional zone

These features may be classified as focal, diffuse, or mixed, supporting differentiation between localized and generalized forms of the disease (**Figure 4**).

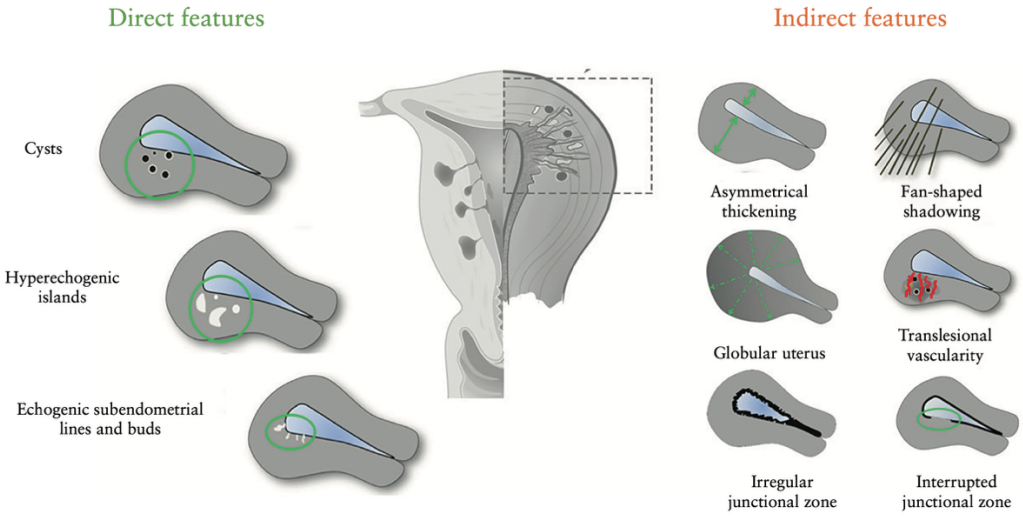

Figure 3. Schematic overview of ultrasound criteria for adenomyosis (MUSA), distinguishing direct signs from indirect signs.

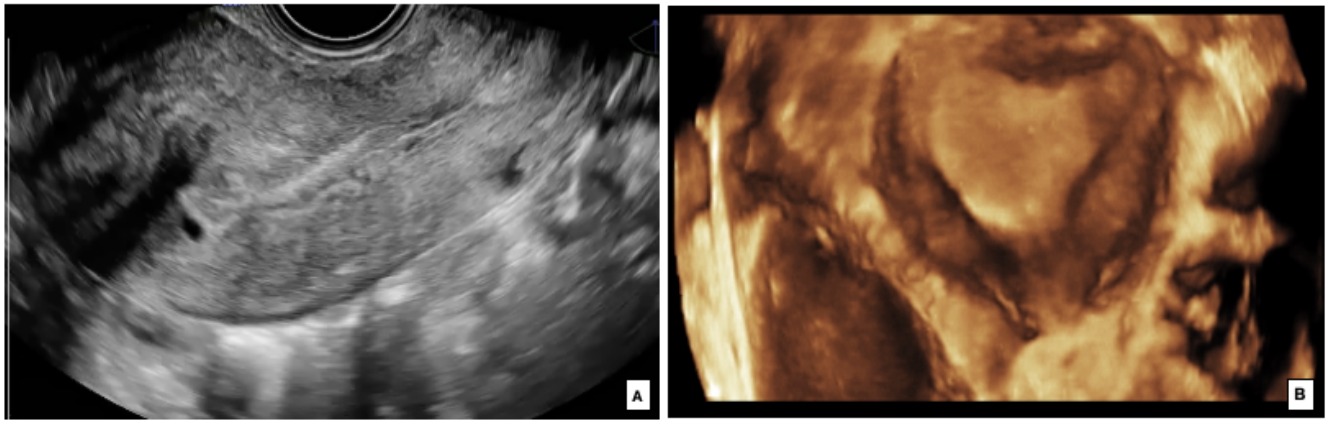

Figure 4. Transvaginal ultrasound findings consistent with adenomyosis.

A) Two-dimensional transvaginal ultrasound showing a heterogeneous myometrium with ill-defined hypoechoic areas, asymmetric thickening, and a small intramyometrial cystic lesion, consistent with focal adenomyosis. The loss of the normal junctional zone definition and the presence of myometrial cysts represent typical sonographic markers of adenomyosis. B) Three-dimensional surface rendering of the uterus, highlighting the irregular myometrial architecture and focal distortion corresponding to the adenomyotic area. The 3D reconstruction enhances visualization of the spatial extent of the lesion and its relationship with the surrounding myometrium, supporting the diagnosis of adenomyosis with cystic component.

With regard to adnexal evaluation, ultrasound identification of an endometrioma has relevant clinical implications, as it may be considered the "tip of the iceberg" of endometriosis. Its presence may conceal deep lesions involving the posterior pelvic compartment, with possible obliteration of the pouch of Douglas, representing the most hidden and complex portion of this "iceberg" [76]. On transvaginal ultrasound, the typical appearance of an endometrioma, observed in approximately 73–82% of cases [81], consists of a cystic lesion with regular margins, containing homogeneous hypoechoic material with a characteristic "ground-glass" appearance, indicative of recurrent intracystic hemorrhage. These lesions are usually clearly demarcated from the adjacent ovarian parenchyma and lack papillary projections, solid components, or intralesional vascularization (**Figure 5**) [81, 82].

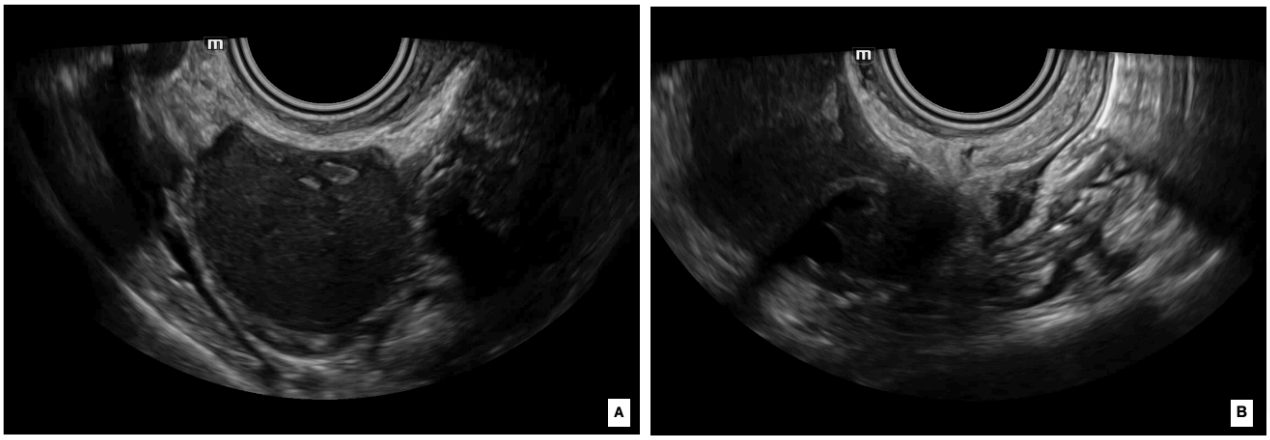

Figure 5. Transvaginal ultrasound images illustrating an ovarian endometrioma associated with deep infiltrating endometriosis of the rectum, supporting the "tip of the iceberg" concept. A) Typical sonographic appearance of an ovarian endometrioma, characterized by a unilocular cystic lesion with homogeneous low-level internal echoes ("ground-glass" echogenicity), well-defined margins, and absence of papillary projections or internal vascularization. B) Adjacent deep endometriotic nodule involving the rectal wall, appearing as a hypoechoic, irregular, solid lesion with loss of normal tissue planes and distortion of the rectosigmoid contour. The coexistence of these findings underscores the role of ovarian endometrioma as a sentinel marker prompting systematic assessment for posterior compartment deep endometriosis.

STEP 2: Assessment of endometriosis "soft markers"

The second step of ultrasound examination involves dynamic evaluation of specific "soft markers," defined as indirect sonographic clues suggestive of endometriosis. Particular attention is paid to localized tenderness, ovarian mobility, and the potential presence of adhesions, especially between the ovaries and the uterus [83].

By applying gentle pressure with the transvaginal probe in the space between the uterus and the ovary, it is possible to assess whether the ovary is fixed to the uterus, lateral pelvic wall, or uterosacral ligaments. Reduced or absent ovarian mobility raises suspicion of adhesive disease. A specific ultrasound sign of advanced pelvic adhesions is the so-called "kissing ovaries sign," observed when

the ovaries appear in close anatomical proximity, often in a retrouterine position, due to extensive adhesions. A recent Italian study proposed a novel potential ultrasound marker for deep endometriosis: the twisting sign, defined as a rotation of the uterine fundus detectable on transvaginal ultrasound. This sign was found to be associated particularly with posterior pelvic compartment involvement, rectosigmoid nodules, uterosacral ligament involvement, ovarian fixation, and absence of the sliding sign, and may reflect distortion of the uterine axis caused by adhesions and endometriotic lesions [84].

STEP 3: Assessment of the sliding sign

The ultrasound sliding sign is a dynamic technique used to evaluate patency of the pouch of Douglas and to identify pelvic adhesions, which are frequently associated with deep endometriosis. The examination varies according to uterine orientation and involves observation of the sliding movement between pelvic structures during probe-induced pressure and concurrent abdominal palpation.

In addition to the classic anterior and posterior sliding signs used to assess endometriosis in the corresponding compartments, medial and lateral variants should also be considered. These are based on evaluation of ovarian mobility relative to both the uterine surface and the pelvic sidewall, providing indirect information on the presence of adhesions involving the ovary and, presumably, the adjacent fallopian tube.

Within the context of tubal evaluation using standard ultrasound, a negative sliding sign increases suspicion of adnexal adhesions; in this setting, ovarian fixation may represent an indirect sign of an inflammatory-adhesive process involving the adjacent tube [85].

This simple and non-invasive technique has demonstrated high sensitivity (83%) and specificity (97%) for the preoperative diagnosis of adhesions and endometriotic involvement of pelvic compartments [86, 87].

STEP 4: Assessment of deep endometriosis nodules

• **Anterior compartment:** includes the urinary bladder, distal ureters, vesicovaginal septum, vesicouterine pouch, and round ligaments. Deep endometriosis involving the bladder appears

sonographically as a well-defined hypoechoic lesion, with or without uterovesical adhesions. Lesions are most commonly located at the bladder base and dome (**Figure 6**). Adequate visualization requires moderate bladder filling (100–150 mL of urine), which helps reduce false-negative findings.

The diagnosis of bladder endometriosis is confirmed when the muscular layer of the bladder wall is involved, showing irregularity or hypoechoic thickening [88, 89].

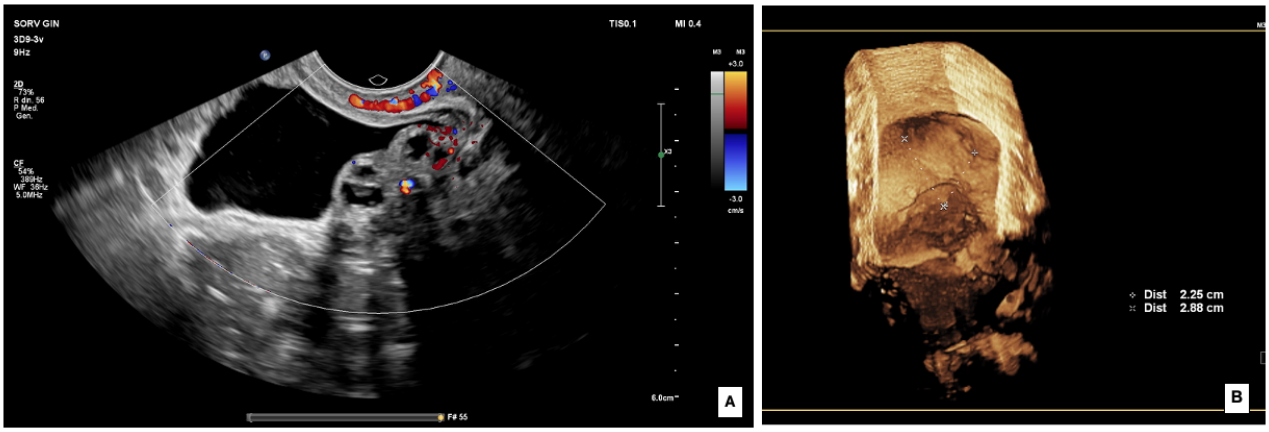

Figure 6. Transvaginal ultrasound findings of a bladder dome endometriotic nodule. (A) Two-dimensional grayscale and color Doppler transvaginal ultrasound demonstrating a solid, hypoechoic, irregularly contoured lesion arising from the bladder dome, measuring approximately 32 × 18 mm. The nodule shows ill-defined margins, heterogeneous echotexture, and moderate internal vascularization on color Doppler, consistent with the typical sonographic appearance of deep infiltrating endometriosis. (B) Three-dimensional surface rendering of the lesion, allowing spatial assessment of its relationship with adjacent pelvic structures. The 3D reconstruction enables estimation of the distance between the nodule and both ureteral orifices, providing additional anatomical information relevant for preoperative planning.

• **Posterior compartment:** the most frequent lesions are located in the rectovaginal septum, pouch of Douglas, and retrocervical region. These lesions are visualized by positioning the probe in the posterior vaginal fornix and appear hypoechoic, non-compressible, and avascular. When

endometriosis involves the uterosacral ligaments, it manifests as hypoechoic thickening in the retro-uterine area, sometimes extending to the vagina and adjacent structures such as the anterior rectal wall [88, 89].

Ultrasound Diagnosis of Bowel Endometriosis

The role of transvaginal ultrasound in the diagnosis of bowel endometriosis warrants specific consideration. This imaging technique represents a highly accurate diagnostic tool for the assessment of rectosigmoid endometriosis, with a reported sensitivity of 91% and specificity of 97% according to a recent meta-analysis including 19 studies [78].

Bowel endometriotic lesions typically appear as focal hypoechoic thickenings or solid hypoechoic nodules, often with irregular margins and absent peripheral or central vascularization. In more advanced cases, lesions may assume a characteristic “diabolo-like” configuration due to adhesion of two opposing foci. Additional specific sonographic signs have been described, including the “comet tail” and the “Indian headdress sign,” which are associated with retraction and distortion of the mucosal folds [88, 89].

Bowel endometriosis is characterized by frequent multifocality and a tendency to cause luminal stenosis, with potential deep involvement of the bowel wall. The distance from the anal verge represents a key parameter for surgical planning. Evaluation of the sliding sign allows assessment of mobility between the uterus and rectum, suggesting the presence of posterior adhesions.

Accurate ultrasound identification of rectosigmoid lesions is essential for precise staging and surgical planning, which may require multidisciplinary collaboration between gynecologic and colorectal surgeons to ensure appropriate management in cases of deep intestinal involvement (**Figure 7**).

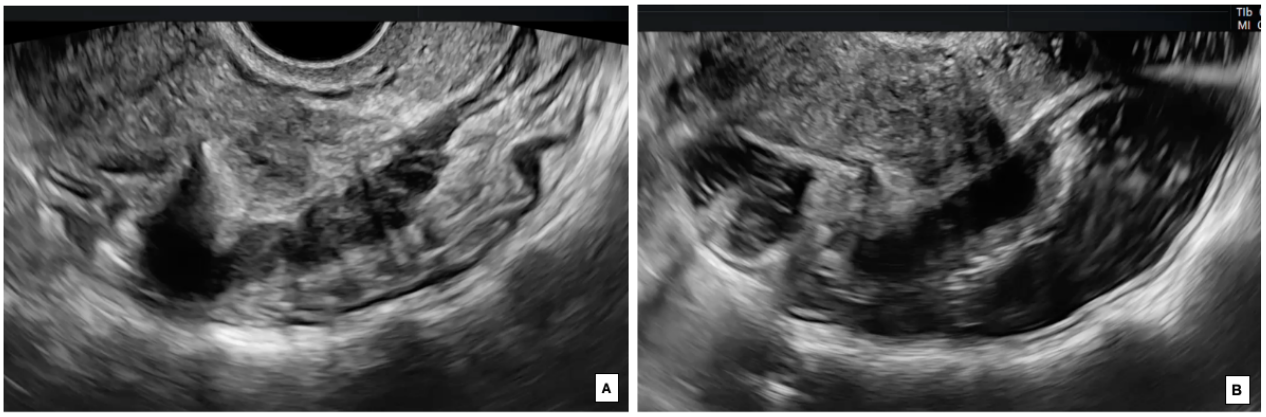

Figure 7. Transvaginal ultrasound appearance of a rectal deep endometriotic nodule, evaluated without (A) and with rectal distension using saline solution (B). A) At conventional non-distended transvaginal ultrasound, the lesion appears as a hypoechoic, irregular, solid mass involving the anterior rectal wall, with ill-defined margins and distortion of the normal layered architecture, consistent with deep infiltrating endometriosis. Visualization of the lesion–rectal interface is limited due to partial collapse of the rectal lumen. B) Following rectal distension with saline solution, the rectal lumen becomes clearly delineated, allowing improved visualization of the depth of infiltration, longitudinal extension, and relationship between the nodule and the muscularis propria. The technique enhances contrast between the lesion and surrounding tissues, facilitating more accurate assessment of lesion size, depth of bowel wall involvement, and surgical planning.

Ultrasound Diagnosis of Parametrial Endometriosis

The parametrium represents a complex anatomical region, classically divided into anterior, lateral, and posterior portions. The anterior parametrium, also referred to as the “vesical pillar,” is surgically defined through dissection of the vesicouterine septum and development of the medial and lateral paravesical spaces. The ureter constitutes a constant anatomical landmark, dividing the pillar into a cranio-medial component, corresponding to the vesicouterine and vesicovaginal ligaments, and a caudo-lateral portion associated with the lateral vesical ligament.

The lateral parametrium extends between the cervix and the lateral pelvic wall, involving the paravesical and pararectal spaces. In this region as well, the ureter delineates a boundary between the cranio-medial component, aligned with the cardinal ligament, and the caudo-lateral portion, corresponding to the paracervix. Within this area course the uterine vessels and, more deeply, connective, lymphatic, and neural structures, separated by the deep uterine vein, which serves as a constant anatomical landmark.

The posterior parametrium is organized around three main ligamentous structures: the uterosacral ligaments, the rectovaginal ligaments, and the lateral rectal ligaments. These are not merely supportive elements, but contain extensions of the superior hypogastric plexus, hypogastric nerves, and splanchnic nerves, as well as pelvic plexuses, thus playing a crucial role in conveying visceral autonomic innervation [76].

From a diagnostic perspective, transvaginal ultrasound is currently considered the first-line modality for the evaluation of endometriosis [90]. The IDEA group defined a standardized four-step ultrasound evaluation protocol [83], which initially did not include a specific assessment of the parametrium. A subsequent systematic review demonstrated that transvaginal ultrasound exhibits high specificity (98%) but limited sensitivity (31%) for parametrial lesions, highlighting the need for greater terminological and technical standardization [91].

To address these limitations, several studies have focused on characterizing the role of ultrasound in parametrial endometriosis. One such study demonstrated the validity of a predictive model based on the combination of concomitant deep endometriosis nodules and indirect sonographic signs, achieving a diagnostic accuracy of 82.1% (AUC 0.75) [92]. Subsequently, a detailed ultrasound description of the three parametrial districts was proposed [93] and later incorporated into an IDEA addendum [94]. Ultrasound techniques involve progressive assessment of the ureters, vesicouterine and vesicovaginal ligaments, the intersection between the ureter and the uterine artery, and posterior structures such as the uterosacral and rectovaginal ligaments, using both sagittal and transverse

planes. It has also been reported that excessive pressure applied with the probe may alter ligament position and reduce diagnostic accuracy [76].

A further study confirmed the validity of transvaginal ultrasound in diagnosing parametrial endometriosis, reporting a sensitivity of 77.1% and a specificity of 99.1% in a large patient cohort [95]. Parametrial lesions typically exhibited irregular margins, stellate morphology, hypoechogenicity, and poor vascularization (**Figure 8**). The posterior parametrium was most frequently involved, followed by the lateral parametrium and, less commonly, the anterior parametrium. Women with parametrial nodules more often presented concomitant rectal or rectovaginal septum nodules, as well as indirect signs such as absence of the sliding sign or ovarian fixation to the uterus.

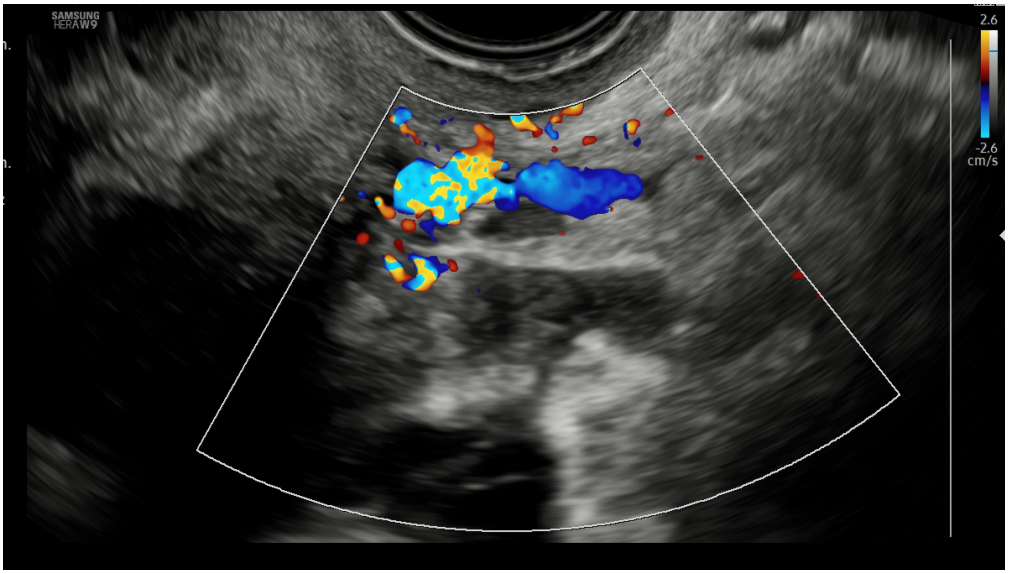

Figure 8. Endometriosis in the lateral parametrium. This image shows a nodule with blurred, irregular margins and mild hypoechogenicity, which extends to infiltrate the uterine vascular plane (evidenced at Color Doppler), altering the normal anatomy. These features are highly suggestive of deep endometriosis involving the parametrium.

6.3.2 Modified Transvaginal Ultrasound Techniques

Transvaginal ultrasound with rectal contrast, also known as rectovaginography, involves the introduction of ultrasound gel or sterile saline solution into the rectal ampulla, with the aim of distending the bowel lumen and improving ultrasound wave transmission. This technique enhances image quality and allows a more accurate evaluation of the rectum and sigmoid colon, improving detection of bowel endometriotic lesions and enabling more precise assessment of lesion extent and depth of infiltration. In addition, this examination facilitates identification of luminal stenosis or narrowing, which may be difficult to document with standard ultrasound, and allows a stratigraphic analysis of the bowel wall: the serosal layer appears thin and hyperechoic, the muscularis propria hypoechoic, while smooth muscle fibers are separated by thin hyperechoic lines corresponding to natural cleavage planes. This detailed characterization permits clearer distinction between infiltrating lesions and surrounding tissues, thereby increasing diagnostic accuracy [96].

Sonovaginography represents an extension of conventional transvaginal ultrasound aimed at improving assessment of the posterior pelvic compartment. The technique involves the introduction of ultrasound gel or sterile saline solution into the vagina using a syringe with a conical tip, resulting in distension of the vaginal walls and fornices and the creation of an acoustic window that enhances contrast and definition of adjacent structures. This approach enables more detailed analysis of the vaginal walls, anterior and posterior fornices, and the rectovaginal septum, areas frequently involved in deep endometriosis. By improving diagnostic sensitivity compared with standard ultrasound, sonovaginography has proven particularly advantageous in cases of suspected posterior disease localization and therefore represents a valuable tool for both surgical planning and accurate clinical assessment of patients [97, 98].

6.3.3 Transabdominal Ultrasound

Transabdominal ultrasound represents a useful tool in the management of patients with suspected endometriosis, although it has inherent limitations. This modality primarily allows detection of secondary changes related to endometriotic infiltration rather than direct visualization of lesions. In

particular, it enables identification of indirect signs of ureteral involvement, such as hydronephrosis and calyceal–pelvic dilation, and estimation of the degree of compromise through morphological assessment of the renal calyces, renal pelvis, and parenchymal thickness, which is reduced in cases of chronic damage. However, the ability of transabdominal ultrasound to delineate the entire course of the ureter is limited, making direct identification of endometriotic lesions challenging. By contrast, transvaginal ultrasound allows a more detailed evaluation of the pelvic portion of the ureters, their caliber, and the distance between endometriotic nodules and the ureteral meatus [83].

In the context of abdominal wall endometriosis, transabdominal ultrasound represents the reference imaging modality, as it allows identification of heterogeneous hypoechoic masses, sometimes surrounded by a hyperechoic rim, with hypoechoic lacunae attributable to intralesional hemorrhage and hyperechoic striae secondary to fibrosis. Lesion margins may appear irregular due to infiltration of adjacent tissues, while Color Doppler imaging may reveal peripheral vascularization of the nodule [99].

Therefore, considering the intrinsic limitations of each technique, it is now widely accepted that transabdominal ultrasound should always be used as a complementary modality to transvaginal ultrasound, particularly in patients with suspected deep endometriosis. This integrated approach allows a more comprehensive evaluation not only of the urinary tract and abdominal wall, but also of the relationships between endometriotic lesions and adjacent pelvic structures, thereby improving diagnostic sensitivity, accuracy of preoperative mapping, and appropriateness of therapeutic planning.

6.4 The Role of Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) represents a fundamental diagnostic modality in the evaluation of pelvic endometriosis, particularly during advanced diagnostic work-up aimed at appropriate therapeutic planning. Although transvaginal ultrasound is the first-line imaging investigation, it has inherent limitations, especially in the presence of complex or poorly defined clinical scenarios. In this

context, MRI provides detailed visualization of the entire pelvic cavity, allowing simultaneous assessment of the main anatomical compartments and enabling identification of deep endometriotic lesions as well as evaluation of involvement of adjacent organs. Owing to its high spatial resolution and the availability of dedicated imaging sequences, MRI is particularly valuable in the preoperative setting for accurate disease staging. A recent meta-analysis reported a sensitivity of 83% and a specificity of 90% for the diagnosis of diffuse deep endometriosis [100].

T2-weighted sequences without fat suppression are essential components of the MRI protocol, as they allow precise identification of lesions across the various pelvic compartments. For ovarian lesions, T1-weighted sequences, both with and without fat suppression, are also useful in differentiating hemorrhagic endometriomas from other masses, such as mature teratomas. T1-weighted fat-suppressed sequences are particularly sensitive for detecting hemorrhagic foci and small peritoneal implants, thereby improving overall disease assessment [101].

In cases of ureteral endometriosis, MRI plays a crucial role in identifying both extrinsic and intrinsic lesions. Extrinsic lesions typically appear as hypointense nodules with foci of hyperintensity on T1- and T2-weighted sequences, whereas periureteral adhesions present as linear hypointense areas. Ureteral infiltration is suspected when no intervening fat plane between the nodule and the ureter is visible on T2-weighted images [96].

MRI is also fundamental in the diagnosis of bowel endometriosis, particularly rectosigmoid involvement, with a reported sensitivity of 85% and specificity of 95% [82]. With the bladder moderately filled and the rectum adequately distended, MRI allows detailed evaluation of intestinal lesions, which typically appear as thickening of the muscular layer.

6.4.1Magnetic Resonance Imaging with Rectal Enema

MRI with rectal enema represents an advanced technique for the evaluation of deep endometriosis involving the rectum and sigmoid colon. Retrograde opacification of the bowel lumen using ultrasound gel allows controlled distension of the distal colon, improving visualization of the bowel

wall and facilitating identification of endometriotic lesions, which tend to mimic the signal intensity of the muscularis propria due to their fibro-muscular composition [102].

Gel administration is performed after adequate bowel preparation and pre-examination fasting, with the aim of reducing peristaltic motion and optimizing image quality. Although the use of antiperistaltic agents varies in clinical practice, luminal distension achieved with gel has been shown to enhance diagnostic sensitivity, as demonstrated by studies reporting a significant increase in lesion detection compared with conventional pelvic MRI (**Figure 9**).

However, MRI with rectal enema presents certain limitations. In particular, it does not allow accurate assessment of the depth of lesion infiltration within the bowel wall and is focused exclusively on the rectosigmoid tract, making it less effective in cases of multifocal disease or lesions located in more proximal colonic segments.

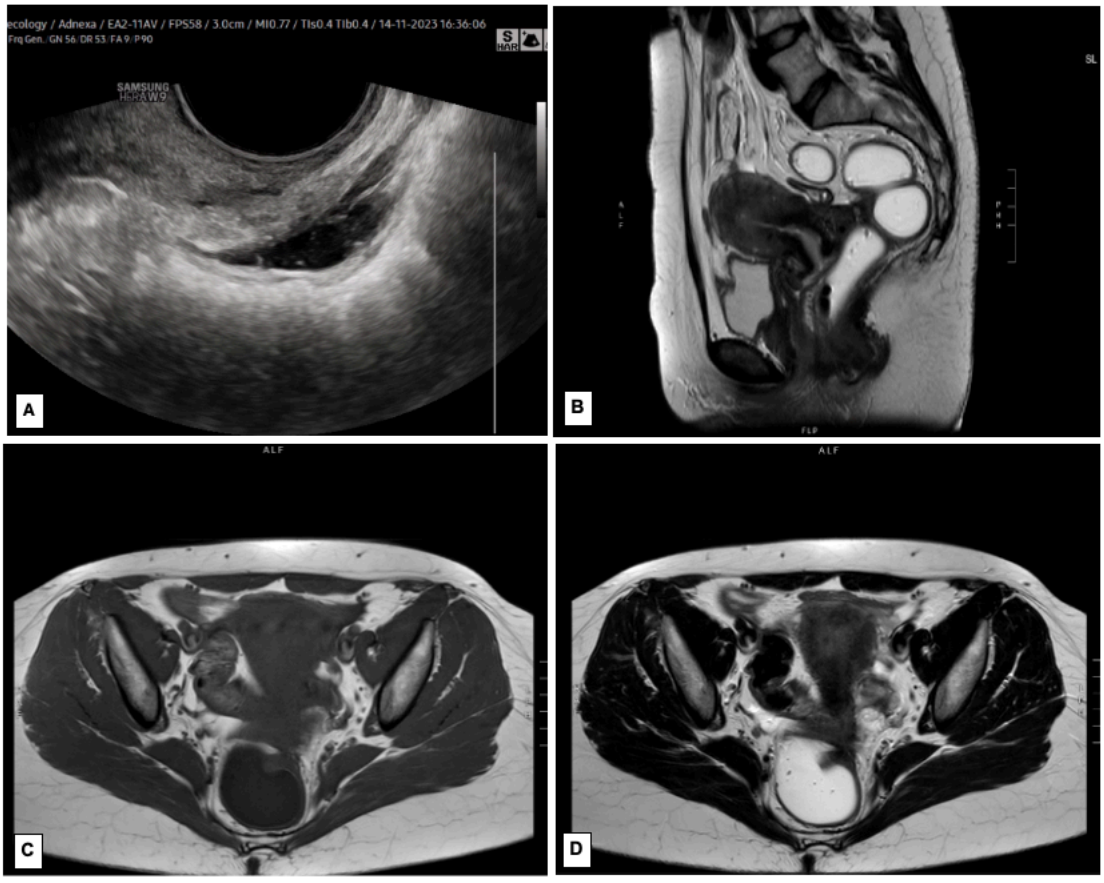

Figure 9. A) Ultrasound – sagittal plane: a medium bowel DE nodule appears as a thickening of the hypoechoic muscularis propria or as hypoechoic nodules, with rare hyperechoic foci and blurred margins. The nodule shows a regular outline (absence of 'spikes'), suggesting the absence of deep infiltration of the (sub)mucosal intestinal layer. A concomitant infiltration of the rectovaginal septum can be observed, reaching the posterior vaginal fornix. B) Fast echo spin (FSE) RMI with T2-weighted (T2W) - sagittal plane; C) FSE-T1W - axial plane; D) FSE-T2W - axial plane: after paramagnetic contrast medium injection there is poor enhancement of the lesion, very similar to the enhancement of the uterus. The infiltration of the muscularis propria can be detected observing the disappearance of the fatty plan between the bowel and the nodule. After lying down on the MR imaging couch, the retrograde distention is performed initially on the lateral decubitus, then on the prone position. A syringe connected to a 20F Foley catheter is used to introduce about 400 mL of ultrasonographic gel diluted with saline solution (1:8) into the rectosigmoid. The distension of recta lumen allows to eveluate the presence of stenosis due to the rectal nodule, which in this case seems to be less than 30%.

6.4.2 Magnetic Resonance Enterography

Entero-MRI (magnetic resonance enterography) represents an advanced technique for the evaluation of bowel endometriosis, particularly for lesions involving the small intestine and colon. Using high-resolution sequences, Entero-MRI enables detailed visualization of the bowel wall and allows identification of endometriotic lesions, which tend to mimic the signal of intestinal musculature due to their fibro-muscular composition. The use of oral contrast agents, such as hyperosmolar solutions (e.g., mannitol), is essential to improve bowel distension, especially in the small intestine and colonic segments, facilitating lesion detection, particularly at the cecum and ileocecal junction.

This technique is particularly useful in the diagnosis of bowel endometriosis, with reported sensitivity up to 96.2% and specificity of 100%, proving more effective than other modalities, such as endorectal

ultrasound and colonoscopy, for lesion detection and assessment of infiltration depth [103]. However, Entero-MRI also has limitations, including difficulty in accurately evaluating lesion infiltration depth in cases of severe or extensive disease and its focus on the small intestine and colon, which does not allow a comprehensive assessment of the entire gastrointestinal tract.

Despite these limitations, Entero-MRI represents an essential diagnostic resource for preoperative planning in bowel endometriosis. Its ability to provide detailed images of the bowel wall is particularly valuable for identifying small lesions and determining their extent, thereby enabling targeted and minimally invasive surgical interventions.

6.5 Double-Contrast Barium Enema

The double-contrast barium enema was one of the earliest tools used for the diagnosis of bowel endometriosis. This examination, which is inexpensive and relatively easy to perform, allows visualization of alterations in the intestinal wall profile, such as luminal stenosis, shortening and deformity of the bowel wall, as well as the characteristic mucosal irregularity known as “crenulation,” considered an indirect sign of deep infiltration [104].

Available data in the literature report heterogeneous results regarding its diagnostic accuracy. In a series of 198 women, double-contrast barium enema achieved a sensitivity of 96.4% and a specificity of 100%, results comparable to those of transvaginal ultrasound with rectal contrast [105]. Variability in reported outcomes may reflect the operator-dependent nature of the examination.

6.6 Computed Tomography

Computed tomography (CT) may represent a useful diagnostic adjunct to MRI, particularly in patients with suspected obstructive uropathy secondary to advanced endometriosis or in the presence of extrapelvic forms, which are rare but well-documented and may involve sites such as the diaphragm, thorax, or abdominal wall. Although CT is not a first-line modality for the evaluation of pelvic disease, it may incidentally reveal endometriomas as ancillary findings during examinations

performed for other indications. The main limitation of CT enema remains the use of ionizing radiation, a particularly relevant concern in young women of reproductive age.

On CT, endometriomas appear as cystic lesions with variable attenuation, ranging from markedly hyperdense to mildly hypodense relative to water, depending on the degree of hemoglobin degradation. In some cases, a thickened wall with a fibrotic component may be observed. Differential diagnosis with simple hemorrhagic cysts may be challenging, as the latter are typically solitary and exhibit smoother contours.

In the setting of acute abdominal pain, CT may detect rare complications such as bleeding due to rupture of an endometrioma into the pelvic cavity. Although uncommon, this event should be considered in the clinical–radiological differential diagnosis.

CT with retrograde enema (CT enteroclysis or "CT enema") is a radiological technique used in the evaluation of bowel endometriosis, particularly for identifying lesions involving the colon and intestinal loops. It involves retrograde distension of the colon through the administration of 2–3 liters of warm water, followed by volumetric contrast-enhanced scanning from the diaphragmatic region to the pubis. This technique allows detailed assessment of bowel endometriosis, with reported sensitivity of 98.7% and specificity of 100% for lesion detection [106].

CT enema is capable of identifying even small serosal lesions, recognizing nodules located in the cecum or terminal ileal loops, and assessing the depth of infiltration within the bowel wall with good accuracy. However, comparative data with MRI combined with luminal distension using ultrasound gel suggest equivalent diagnostic accuracy between the two techniques. Furthermore, a prospective study confirmed that CT enema and distensive MRI demonstrate similar performance in identifying multifocal and multicentric lesions [107].

Uro-CT (CT urography) should be specifically considered when ureteral endometriosis or endometriosis-related extrinsic compression is suspected, particularly in the presence of hydronephrosis/hydroureter on ultrasound or declining renal function. Uro-CT provides a comprehensive evaluation of the urinary tract by confirming the presence and grade of

hydroureteronephrosis, identifying the level of ureteral narrowing (often at the crossing with the uterine artery or within the parametrial tunnel), and documenting delayed excretion or reduced function of the affected kidney. Moreover, multiplanar and 3D reconstructions improve depiction of the ureteral course and the relationship between stenosis and adjacent pelvic structures, thereby supporting surgical planning and multidisciplinary decision-making (e.g., ureterolysis, segmental ureteral resection with reimplantation, or stenting) (**Figure 10**).

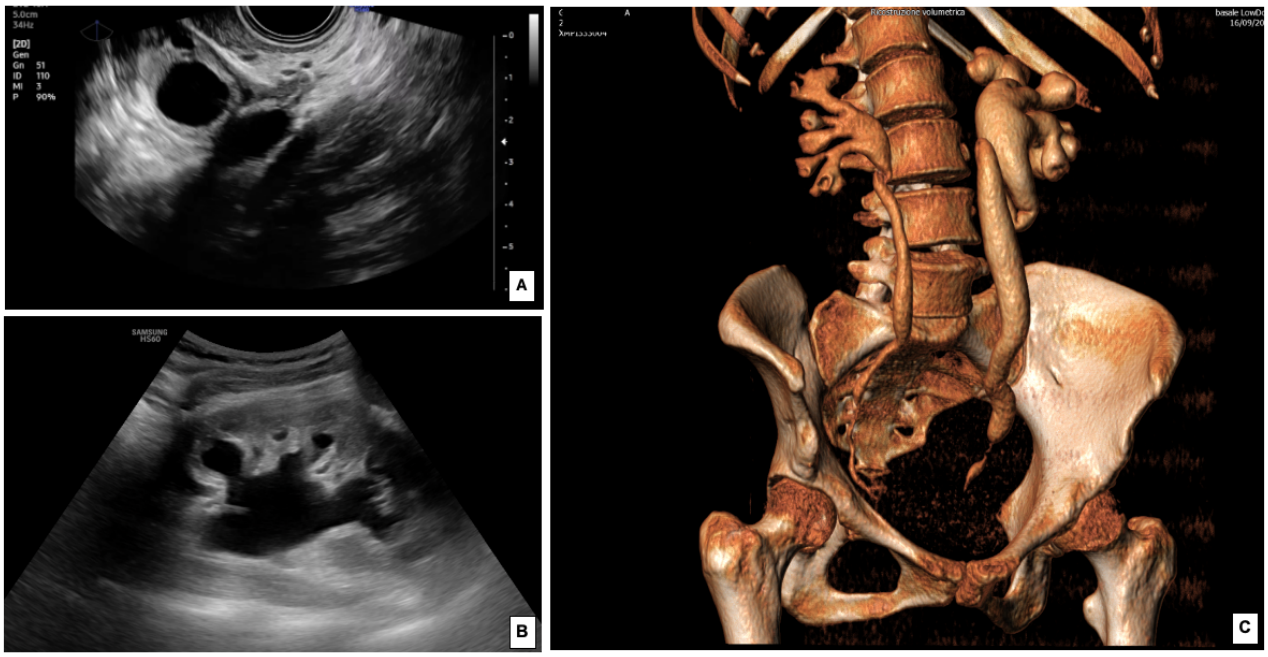

Figure 10. A) A lateral parametrial endometriotic nodule, is identified, displacing the ipsilateral ovary medially and infiltrating the ureter at its crossing with the uterine artery, leading to ipsilateral hydroureteronephrosis. Transvaginal ultrasound shows upstream ureteral dilatation consistent with obstructive uropathy. B) Transabdominal ultrasound confirms the obstruction by demonstrating dilatation of the renal collecting system (calyceal/pelvicalyceal ectasia). C) Uro-CT (CT urography) with 3D reconstruction confirms ipsilateral hydroureteronephrosis and delineates the level of ureteral narrowing.

6.7 Renal Scintigraphy

In the presence of significant hydronephrosis detected by ultrasound or MRI, renal scintigraphy is indicated to assess residual renal parenchymal function. This investigation assists in guiding the choice between a conservative approach and radical intervention [108]. Nephrectomy is recommended in cases where renal function is reduced below 10–15%, or in the presence of complications such as persistent pain, renal lithiasis, renovascular hypertension, or recurrent urinary tract infections [109].

6.8 The Role of Biomarkers

Currently, no available biomarker fully meets the criteria required for a reliable diagnosis of endometriosis, including high sensitivity and specificity, reproducibility, accessibility, and cost-effectiveness. For this reason, biomarkers, although an area of growing interest, are mainly used as an adjunct to conventional diagnostic techniques.

Serological biomarkers are the most widely used in clinical practice. Among these, CA125 is the most extensively studied marker. Encoded by the MUC16 gene, it is physiologically expressed by mesothelial tissues such as the fallopian tubes, peritoneum, and endocervix. Although CA125 is traditionally associated with ovarian carcinoma, it may also be elevated in benign conditions, including endometriosis, particularly in the presence of extensive implants or adhesions. However, serum levels are generally lower than those observed in malignancies. The diagnostic value of CA125 alone is limited due to its low specificity; therefore, its measurement is often combined with other markers, such as HE4 and CA72-4, to improve discrimination between benign disease and neoplastic conditions [110, 111].

The combination of biomarkers has led to the development of composite indices such as ROMA ("Risk of Ovarian Malignancy Algorithm"), which integrates CA125 and HE4 levels with clinical data such as age and menopausal status, achieving a sensitivity of 81% and a specificity of 75% in distinguishing benign from malignant masses [112].

Another useful tool is the IOTA-ADNEX model, which combines ultrasound, clinical, and serological data to provide a predictive assessment of the nature of adnexal masses [113].

Beyond traditional tumor markers, molecules belonging to the glycoprotein family, such as Activin A and Follistatin, have also been investigated. Activin A has been found to be overexpressed in ectopic endometriotic tissue, although its serum levels do not differ significantly from those of controls. Conversely, Follistatin has been shown to be increased in the blood of patients with ovarian endometriosis, demonstrating sensitivity and specificity exceeding 90% in some cohorts [114]. Glycodelin A, an immunosuppressive glycoprotein produced by the endometrium, is also elevated in both serum and peritoneal fluid of affected patients, and its overexpression has been associated with impaired fertility [115].

The immunological alterations observed in endometriosis have prompted investigation of numerous cytokines and inflammatory molecules as potential biomarkers. IL-6 is elevated in the serum of patients with moderate disease, while TNF-α is increased in peritoneal fluid and correlates with disease severity. Despite these findings, the clinical use of these markers remains limited due to the lack of standardized reference values [116].

More recently, attention has focused on the analysis of microRNAs (miRNAs), small non-coding RNAs that regulate post-transcriptional gene expression. In particular, certain miRNAs, such as miRNA-31, -145, -122, and -199a, are overexpressed in the plasma of women with endometriosis, whereas others, including miRNA-145 and 543-3p, show reduced expression. Although promising, these findings require further validation before clinical application [117].

Urinary biomarkers, while representing an ideal solution due to ease of collection and analysis, have not yet achieved satisfactory diagnostic performance. Molecules such as cytokeratin 19 fragments (CYFRA 21-1), enolase 1, and vitamin D binding protein (VDBP) have shown alterations in some patient cohorts, but without sufficient accuracy for clinical implementation [118]. Similarly, mass spectrometry-based studies aimed at identifying specific urinary proteomic patterns have not yet

identified a single biomarker or molecular panel capable of providing adequate sensitivity and specificity.

7. MEDICAL THERAPY

7.1 First-Line Medical Therapy

The primary objective of pharmacological therapy in endometriosis is the treatment of pain-related symptoms associated with the disease. In addition, the therapeutic approach aims to reduce the risk of postoperative recurrence and, presumably, to limit long-term disease progression. This therapeutic strategy also contributes to improving patients' quality of life by reducing the impact of pain and daily functional limitations.

7.1.1 Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent the main non-hormonal therapeutic approach for the management of dysmenorrhea and endometriosis-related pelvic pain [119]. Despite their widespread use in clinical practice, the effectiveness of NSAIDs in this setting is not supported by high-quality evidence, and to date no specific molecule has demonstrated significant superiority in the treatment of pain associated with the disease [120].

7.1.2 Estroprogestins and Progestins

First-line medical treatment for endometriosis is based on the use of estroprogestins or progestins, which can be administered through different routes (oral, vaginal ring, subcutaneous) and according to cyclic or continuous regimens [121].

The therapeutic efficacy of these agents in endometriosis management is mainly related to ovulation inhibition, mediated by suppression of ovarian E2 and progesterone secretion through an anti-gonadotropic effect. These drugs reduce menstrual flow, promote decidualization of endometriotic implants, and modulate cellular processes by inducing apoptosis and inhibiting proliferation [122]. A direct anti-inflammatory activity of progestins on ectopic tissues has also been documented. A recent systematic review demonstrated that treatment with combined estroprogestins, administered either cyclically or continuously, results in a clinically and statistically significant reduction in pain compared with baseline values [123].

COC represent the only pharmacological option currently shown to be effective in reducing the risk of ovarian endometrioma recurrence after surgical excision, with evidence suggesting greater efficacy of continuous compared with cyclic administration in reducing dysmenorrhea, although without a significant impact on endometrioma recurrence rates [124]. Although data on the use of vaginal rings and transdermal patches are limited, available evidence indicates comparable effectiveness to COC in pain management [125].

Progestins represent an effective therapeutic option for controlling endometriosis-related pain, including in cases with comorbidities such as migraine or rectovaginal involvement, with outcomes comparable to those achieved with COC [126].

Among progestins, dienogest (2 mg/day) is currently considered the reference compound, owing to robust evidence of clinical efficacy and quality-of-life improvement derived from randomized and cohort studies [127]. Dienogest, characterized by high selectivity for progesterone receptors and antiandrogenic activity, is associated with a favorable metabolic profile.

Norethisterone acetate (NETA), an oral progestin derived from 19-nortestosterone, represents an effective option for long-term treatment of endometriosis, improving both pelvic pain and associated bowel symptoms [128, 129].

Depot medroxyprogesterone acetate and subcutaneous implants have also proven effective in reducing pain symptoms while maintaining a good safety profile [130]. In addition, the levonorgestrel-releasing intrauterine system offers a long-term therapeutic option, although its use may be limited by adverse events such as irregular bleeding, mood changes, and uncertainty regarding its effectiveness in preventing endometrioma recurrence. **Table 1** shows adverse effects of progestins used in the treatment of endometriosis.

Progestin therapy	**Most frequently reported side effects**	**Notes on tolerability**
Medroxyprogesterone acetate	Weight gain, edema, spotting/amenorrhea, acne, mood changes, decreased libido	Long-acting formulation; higher rates of amenorrhea and fluid retention
Dienogest	Irregular bleeding (especially in early treatment), headaches, weight changes, mood alterations	Generally well tolerated; maintains stable estradiol levels
Norethindrone acetate	Weight gain, acne, breast tenderness, libido reduction, lipid profile changes	Common in continuous low-dose regimens
Desogestrel	Breakthrough bleeding, acne, ovarian cysts	Often used as progestin-only pill; fewer systemic effects
Levonorgestrel-intrauterine device	Irregular bleeding, acne, pelvic discomfort, ovarian cyst formation, mood changes	High local (endometrial) progestin activity with minimal systemic exposure
Etonogestrel implant	Bleeding disturbances, weight gain, decreased libido, headaches	Suitable for long-term contraception and symptom control

Table 1 shows adverse effects of progestins used in the treatment of endometriosis.

7.2 Second-Line Medical Therapy

7.2.1 Gonadotropin-Releasing Hormone (GnRH) Agonists and Antagonists

In the management of patients with symptoms refractory to first-line therapies or following complex surgical interventions, the use of GnRH agonists and antagonists is indicated as second-line therapy. These agents are primarily aimed at preventing disease recurrence in selected cases [7].

GnRH agonists (goserelin, leuprolide, nafarelin, buserelin, triptorelin) act by suppressing ovarian estrogen production, inducing amenorrhea and reduction of endometriotic lesions; however, they may cause adverse events such as loss of bone mineral density, hot flushes, and alterations in lipid profile [131]. To limit these effects, early initiation of "add-back" therapy, such as COCs or NETA, is recommended [132].

A Cochrane review confirmed that GnRH agonists are more effective than placebo in improving endometriosis-related pain symptoms, with outcomes comparable to those achieved with the levonorgestrel-releasing intrauterine system [133]. Moreover, several studies have demonstrated similar analgesic efficacy compared with progestins (such as dienogest or medroxyprogesterone acetate) and COCs, without substantial differences in terms of safety [134].

GnRH antagonists exert their effect through competitive inhibition of pituitary GnRH receptors, resulting in rapid, direct, and dose-dependent suppression of LH and FSH secretion, with consequent reduction in estrogen levels and regression of endometriotic lesions [135]. Unlike GnRH agonists, which induce an initial stimulatory phase (flare-up) followed by receptor downregulation, GnRH antagonists immediately block gonadotropin secretion without an activation phase [136]. This pharmacodynamic profile allows for faster and reversible suppression of ovarian activity, ensuring more flexible control of endometriosis-related symptoms and offering a potential advantage in terms

of tolerability and safety [137]. In particular, this therapeutic strategy enables maintenance of serum E2 levels within a physiologically safe range, minimizing the risk of hypoestrogenism-related adverse events such as bone mineral density loss and vasomotor symptoms [138]. Furthermore, the availability of oral formulations, together with rapid reversibility of the suppressive effect and prompt recovery of ovarian function after treatment discontinuation, represents an additional clinical advantage [108].

Among the main GnRH antagonists used in the treatment of endometriosis, elagolix, relugolix, and linzagolix differ in terms of pharmacokinetic profile, potency, and management of adverse effects, including those related to bone mineral density and the need for add-back therapy.

Elagolix, an oral GnRH antagonist, has been approved for the treatment of endometriosis and has demonstrated efficacy in reducing pelvic pain and dysmenorrhea [139]. Its effectiveness in alleviating pelvic pain and dysmenorrhea has been confirmed in clinical trials, showing dose-dependent suppression of estrogen production [140]. Administration of elagolix at doses of 150 mg or 200 mg per day leads to reduction of endometriotic nodules but may cause a decrease in bone mineral density, particularly at the higher dose [141]. Currently, the use of low-dose estrogen add-back therapy to prevent bone mineral density loss is under investigation. Common adverse effects include hot flushes, night sweats, and mood disturbances, which are generally reversible upon treatment discontinuation.

Relugolix, also an oral GnRH antagonist, in combination with E2 and NETA, has been approved by the Food and Drug Administration (FDA) for the treatment of endometriosis, based on favorable results from the phase 3 SPIRIT-1 and SPIRIT-2 clinical trials, which demonstrated its efficacy in controlling endometriosis-associated pain [142].

Linzagolix is another oral GnRH antagonist currently under investigation for endometriosis. The EDELWEISS study, conducted in 328 patients, demonstrated that doses ≥75 mg significantly reduced pelvic pain, dysmenorrhea, and dyspareunia compared with placebo, with benefits evident as early as week 12. The 75 mg dose was associated with good efficacy and limited effects on bone mineral density, whereas higher doses (200 mg) required add-back therapy to mitigate bone loss [143].

A recent meta-analysis evaluated the efficacy and safety of the main pharmacological treatments for endometriosis-associated pain, including GnRH antagonists and agonists, dienogest, and oral contraceptives. Results showed that high-dose GnRH antagonists were the most effective in reducing non-menstrual pelvic pain and dysmenorrhea, whereas leuprolide demonstrated the greatest effect on dyspareunia. All treatments were associated with an increased incidence of adverse events compared with placebo, with a more favorable safety profile for dienogest and a less favorable one for GnRH agonists. These findings highlight that therapeutic choice should take into account both the predominant clinical outcome and the safety profile of the selected drug [144]

7.2.2 Emerging Therapies Under Investigation

Current research in endometriosis focuses on the development of effective therapies for patients who are unresponsive to conventional treatments. GnRH antagonists represent the most promising candidates in advanced stages of clinical development. Other hormonal options, such as aromatase inhibitors, are used off-label in selected cases; however, the high incidence of adverse events limits their use in young women.

Selective estrogen receptor modulators (SERM, Selective Estrogen Receptor Modulators) and selective progesterone receptor modulators (SPRM, Selective Progesterone Receptor Modulators), despite encouraging preclinical results, have not yet demonstrated sufficient clinical efficacy or safety.

Finally, novel molecular targets, including steroid sulfatase inhibitors (STS, Steroid Sulfatase) and 17β-hydroxysteroid dehydrogenase type 1 inhibitors (17β-HSD1, 17β-Hydroxysteroid Dehydrogenase Type 1), are currently under evaluation for their potential to reduce estrogenic activity and disease-associated pain [121, 137].

8. SURGICAL THERAPY

The surgical approach should be considered in cases of severe symptoms refractory to medical treatment or in the presence of functional impairment of vital organs. Conditions such as bowel obstruction, hydroureteronephrosis, or ovarian cysts with features suspicious for malignancy represent absolute indications for surgery, aimed at controlling pain, restoring organ function, and preventing long-term complications [7].

8.1 Surgery for Ovarian Endometrioma

The presence of an ovarian endometrioma may impair ovarian reserve [145], and surgical intervention itself may further worsen it [146]. Therefore, careful patient selection is essential, taking into account age, reproductive desire, ovarian reserve, clinical history, and disease severity [147, 148]. In patients at high risk (advanced age, low ovarian reserve, bilateral endometriomas), counseling regarding fertility preservation is recommended [149].

Cystectomy represents the standard surgical technique and is associated with lower recurrence rates and better symptom control compared with ablation [150]. It consists of “stripping” of the cyst wall, which is separated from the ovarian parenchyma through traction and countertraction using atraumatic forceps [151]. The procedure typically begins at the site of adhesion, often corresponding to the area of cyst rupture, where the cyst wall is thinner and more adherent. The cleavage plane is identified and followed along the remaining cyst wall.

At the end of the procedure, hemostasis is preferably achieved using bipolar forceps. However, coagulation may damage ovarian reserve, either through removal of follicles adjacent to the cyst or

through vascular compromise if performed near the ovarian hilum. Alternative techniques include suturing of the cyst bed, use of hemostatic sealants, or application of gauze packing [151].

Ablation, performed using CO_2 laser, plasma energy, or electrosurgery (monopolar or bipolar), is based on fenestration, aspiration, and irrigation of the cyst. Energy sources associated with lower thermal spread (plasma, laser) appear to be less damaging to the ovarian parenchyma [152], although a clear benefit in terms of fertility outcomes has not yet been demonstrated.

8.2 Surgery for Parametrial Endometriosis

The surgical management of deep parametrial endometriosis has been described in several videos and studies, often in combination with excision of rectosigmoid nodules [76]. The most established technique for standardized parametrial dissection is the so-called “Negrar method” [153], which is based on the development of precise anatomical planes.

The procedure begins with opening the presacral space of Waldeyer and the retrorectal space of Heald, preferentially working in avascular planes while protecting pelvic sympathetic fibers, including the inferior mesenteric and superior hypogastric plexuses, the superior hypogastric nerves, and the lumbosacral sympathetic trunk. The ureter is isolated as a constant landmark. In the presence of deep endometriosis, lateral parametrectomy is performed while preserving the posterolateral sympathetic fibers and those of the inferior mesorectum, including the inferior hypogastric nerves and the proximal portion of the inferior hypogastric plexus. When feasible, the uterine artery is preserved, and the deep uterine vein serves as a guide to distinguish the vascular from the neural component of the parametrium.

In posterior parametrial nodules, posterior parametrectomy is performed while maintaining the integrity of the deep uterine veins, parasympathetic splanchnic nerves, and the cranial and middle portions of the inferior hypogastric plexus, preserving caudal structures within the posterolateral ligaments and paravaginal planes [154-156]. Systematic transection of the internal iliac artery and vein is avoided to prevent compromise of pelvic perfusion, whereas small splanchnic nerves are

transected only if infiltrated by fibrotic nodules, thereby reducing the risk of sexual, bladder, rectal, or sensory dysfunctions [157].

For anterior parametrium involvement, the medial and lateral paravesical spaces, the retropubic space of Retzius, and the space of Bogros are systematically developed, always working within healthy tissue. This approach allows targeted resections, management of ureteral strictures, and mobilization or incision of the bladder when necessary, ensuring radical excision of anterior deep endometriosis [158].

8.3 Surgery for Intestinal Endometriosis

It is widely documented that radical excision of intestinal endometriotic lesions allows for a significant improvement in pain-related symptoms [159, 160]. The recommended surgical approach is minimally invasive and should be performed in referral centers with experienced multidisciplinary teams (gynecologists, general surgeons, urologists), in order to optimize clinical outcomes and reduce the incidence of complications. The main postoperative complications involve pelvic visceral dysfunctions, particularly rectal, bladder, and sexual dysfunctions. However, with the introduction and progressive dissemination of nerve-sparing techniques, the incidence of these neurological complications has markedly decreased without compromising the radicality of surgical treatment [153]. In infertile patients, the decision-making process must take into account age, ovarian reserve, and disease extent, as severe intraoperative complications may negatively affect spontaneous or assisted reproductive outcomes [161].

Surgical techniques are broadly classified into conservative (shaving, disc excision) and non-conservative (segmental bowel resection). The choice of the most appropriate technique is based on careful preoperative and intraoperative assessment of lesion characteristics, surgeon expertise, and patient preferences.

Rectal shaving (also referred to as nodulectomy), first described in 1991 by Reich et al., involves removal of the infiltrating lesion down to the muscular layer of the rectum [162].

Disc excision is indicated for unifocal nodules <30 mm with circumferential involvement <50–60% and without high-grade stenosis [163, 164]. This technique employs a circular mechanical stapler introduced transanally to excise the anterior and lateral bowel wall down to the muscularis or submucosa.

Segmental resection consists of removal of an intestinal segment (typically rectosigmoid) followed by end-to-end anastomosis, with or without a protective stoma. It is indicated in the presence of nodules infiltrating the full thickness of the intestinal wall (inner muscularis and/or mucosa), in cases of severe stenosis, multiple nodules of the sigmoid or rectosigmoid junction, or nodules >30 mm reaching the outer muscular layer.

In particularly complex scenarios characterized by parametrial infiltration, segmental resection may entail a high risk of visceral nerve dysfunction. To address this issue, nerve-sparing techniques have been developed and are now standardized and internationally recognized, including the "Negrar method" [153]. These techniques aim to identify and preserve visceral nerve fibers and their surgical landmarks, significantly reducing the risk of bladder, rectal, and sexual dysfunctions while maintaining adequate surgical radicality.

8.4 Surgery for Urinary Tract Endometriosis

With regard to the treatment of bladder endometriosis, management is predominantly surgical and aims at complete disease removal in a single procedure, resulting in significant improvement in pain-related symptoms [165].

The reference technique is partial cystectomy, which can be performed via laparotomy or laparoscopy, with the latter being preferred due to shorter recovery time and reduced postoperative pain [166, 167]. Robotic surgery is increasingly gaining a role in this setting [168]. As bladder endometriosis typically infiltrates the muscular layer, excision of the infiltrated tissue, including the detrusor muscle and the overlying urothelium, is required, followed by reconstruction of the bladder wall.

Transurethral resection represents an additional option; however, available data are limited and indicate higher rates of recurrence, symptom persistence, and risk of bladder perforation [169]. This approach is limited by the pathophysiology of the disease, which originates from the outer bladder surface, making complete resection from within difficult; therefore, it is not recommended as a first-line treatment.

Combined techniques, associating a transurethral approach with laparoscopic, laparotomic, or robotic surgery, may be useful in the case of large lesions to facilitate identification of margins and reduce the invasiveness of resection [170].

In the treatment of ureteral endometriosis, the main objectives are resolution of obstruction and prevention of recurrence. The choice of technique depends on disease extent and residual renal function. Surgical options include ureterolysis (conservative approach), ureteral resection with end-to-end anastomosis, ureteral reimplantation into the bladder, and, in extreme cases, nephroureterectomy. All these techniques can be performed via laparotomy, laparoscopy, or robotic surgery.

Ureterolysis consists of mobilization and release of the ureter from fibrotic tissue and is indicated in cases of non-obstructive extrinsic disease, with laparoscopy being the preferred approach [171].

In the presence of severe obstruction, ureteral resection with anastomosis allows complete excision of the disease and perilesional tissue but is associated with complications, including strictures and anastomotic dehiscence [172].

Ureteral reimplantation is indicated when the lesion involves the distal ureter or a long pelvic segment, making ureteroureteral anastomosis unfeasible, or in cases of recurrent stenosis following conservative procedures [173-175].

Ureteral endometriosis may lead to hydronephrosis, loss of renal function, and, in severe bilateral cases, chronic renal failure. Preoperative placement of a ureteral stent or nephrostomy may improve residual renal function [176]. Renal scintigraphy is useful in the preoperative assessment: renal function <10–15% suggests a low likelihood of recovery and supports indication for

nephroureterectomy [108]. Although official guidelines are lacking, nephroureterectomy may be considered in the presence of reduced renal function, persistent pain, lithiasis, recurrent infections, or renovascular hypertension [109], following multidisciplinary evaluation.

9. ENDOMETRIOSIS AND INFERTILITY

The relationship between endometriosis and infertility remains a subject of extensive debate. From a pathophysiological perspective, endometriosis may impair fertility through multiple mechanisms, whose relative contribution varies according to disease severity. According to the American Society for Reproductive Medicine classification, endometriosis is divided into four stages: minimal (I), mild (II), moderate (III), and severe (IV), based on lesion location and type and the presence of adhesions, particularly involving the pouch of Douglas [70].

In advanced forms (stages III–IV), infertility is mainly related to well-documented mechanisms, including distortion of pelvic anatomy induced by chronic inflammation and ovarian damage secondary to the presence of endometriomas. Conversely, in milder cases (stages I–II), the pathogenic role remains less clearly defined [177]. Several hypotheses have been proposed, including alterations in cytokine profiles, mechanical or inflammatory effects of ovarian lesions, tubal motility dysfunction, toxic effects of peritoneal fluid on gametes and embryos, abnormalities of myometrial contractions, and alterations of the endometrial environment.

In particular, in mild and moderate disease, inflammation of the peritoneal fluid appears to play a relevant role in impairing gamete and embryo quality [178]. An additional obstacle to fertility may derive from dyspareunia, which is frequent in women with advanced endometriosis and may reduce the frequency of intercourse targeted at conception.

Overall, endometriosis may interfere with fertility through tubal alterations (reduced oocyte transport capacity due to inflammatory cytokines), endometrial changes (gene expression modifications

hindering implantation), and ovarian dysfunction (reduced functional reserve due to inflammatory damage, cysts, or surgical sequelae) [179].

Management of infertility in women with endometriosis should initially consider the possibility of spontaneous conception. Medical therapies (combined estrogen–progestins, progestins, GnRH agonists and antagonists), although effective for symptom control, do not improve spontaneous fertility and are therefore not recommended for this purpose [180].

Conversely, operative laparoscopic surgery has demonstrated efficacy in improving spontaneous pregnancy rates in women with stage I or II endometriosis, particularly when complete excision of lesions and adhesiolysis are performed [180]. In more advanced stages (III–IV), the effectiveness of surgery is less clearly defined; however, restoration of pelvic anatomy is hypothesized to facilitate fertilization and implantation by improving tubal transport.

Removal of endometriomas larger than 4 cm using the stripping technique is associated with improved spontaneous fertility and lower recurrence rates compared with simple drainage and coagulation [150]. Nevertheless, a conservative approach toward healthy ovarian tissue is essential in order to preserve ovarian reserve, especially in the case of bilateral endometriomas, which are associated with an increased risk of premature ovarian insufficiency.

When spontaneous conception does not occur despite adequate surgical treatment, recourse to Assisted Reproductive Technologies (ART) becomes necessary. The main indications include age over 35 years, tubal damage, bilateral endometriomas, reduced ovarian reserve, male factor infertility, or failure to conceive after surgery.

Pre-ART evaluation includes assessment of ovarian reserve (by antral follicle count or AMH measurement), semen analysis, and counseling of the couple to discuss the therapeutic approach and willingness to undertake the treatment pathway [181]. ART techniques are classified into first-level procedures (in vivo fertilization) and second-level procedures (in vitro fertilization with embryo transfer).

Intrauterine insemination (IUI) is a first-level ART technique indicated for women with stage I–II endometriosis, age under 35 years, patent tubes, absence of other infertility factors, and/or dyspareunia limiting sexual intercourse. IUI may be performed in a natural cycle or following ovulation induction. Available evidence, although limited, suggests higher pregnancy rates when IUI is combined with ovarian stimulation.

In vitro fertilization (IVF) is a second-level ART technique indicated in cases of severe endometriosis, tubal damage, moderate-to-severe male factor infertility, age >35 years, or failure of IUI [182]. The protocol includes controlled ovarian stimulation, ultrasound and hormonal monitoring, induction of oocyte maturation, transvaginal oocyte retrieval (pick-up), in vitro fertilization, and embryo transfer into the uterus.

10. ENDOMETRIOSIS AND CANCER

Although endometriosis is neither a malignant condition nor characterized by uncontrolled cellular proliferation, it shares several features with cancer, including the ability to form both local and distant lesions, resistance to apoptosis, and the capacity to invade surrounding tissues, resulting in damage to involved organs [61]. In addition, endometriosis creates a chronic inflammatory environment at both local and systemic levels and has been linked to several risk factors common to certain malignancies [183]. These aspects have fueled a long-standing debate in the literature regarding a potential increased oncological risk in women affected by endometriosis, a topic that has been particularly investigated over the past decade. Epidemiological studies have indeed reported a higher incidence of various cancers in this population. More recently, genetic sequencing analyses have revealed that approximately 20% of endometriotic lesions, both ovarian and deep infiltrating, harbor somatic mutations typical of oncogenic driver events [184], although such genetic alterations have also been detected at high frequencies in the eutopic endometrium of healthy women [185].

Historically, as early as 1925, Sampson hypothesized that endometriosis could evolve into carcinoma; however, only more recently has a form of “atypical endometriosis” been recognized, characterized by cellular alterations suggestive of neoplastic transformation [186]. Histopathological studies have shown that a substantial proportion of endometrioid and clear cell ovarian carcinomas are associated with adjacent foci of atypical endometriosis, supporting the hypothesis of a direct progression pathway [187].

The link between endometriosis and cancer appears to be mediated by complex molecular mechanisms, including chronic inflammation, COX-2 overexpression, and local hyperestrogenism, all of which contribute to the creation of a microenvironment conducive to cellular transformation [188]. Mutation of the ARID1A gene, involved in chromatin remodeling, represents one of the key molecular events in the progression from atypical endometriosis to ovarian carcinoma, as confirmed by genetic studies and experimental models [189]. Additional genetic alterations, such as loss of heterozygosity in genes including p53, RAS, and PTEN, are also implicated in this process [190].

From a clinical perspective, endometriosis is associated with an increased risk of epithelial ovarian cancer, particularly the endometrioid and clear cell histotypes, with a prevalence of endometriosis among patients affected by these tumors higher than that observed in other histological subtypes [191]. Women with endometriosis have an approximately twofold increased risk of developing epithelial ovarian cancer compared with the general population, a risk that appears to rise with disease duration [192]. From a prognostic standpoint, ovarian cancers associated with endometriosis tend to occur at a younger age and at earlier stages, with a generally more favorable prognosis compared with non-associated tumors [193].

A recent meta-analysis reported a variable association between endometriosis and endometrial cancer, with results influenced by substantial heterogeneity among studies and methodological differences in adopted criteria [194]. The analysis indicated a 23% increased risk for women with endometriosis, although this did not reach statistical significance. This estimate is consistent with that reported by Li et al., who described a 17% increased risk, but differs from the conclusions of Gandini

et al., who identified a stronger and statistically significant association of 38% [195, 196]. A possible explanation for the heterogeneity among meta-analyses lies in differences in study inclusion strategies, particularly regarding control for potential confounding factors. Among these, body mass index represents a crucial variable, as women with a lean body habitus are known to have a higher risk of developing endometriosis [183], whereas overweight and obesity are well-established risk factors for endometrial carcinoma [197].

Of particular interest is the inverse association observed between endometriosis and cervical cancer, which may reflect a diagnostic bias related to increased clinical surveillance and screening among women with endometriosis, rather than a true protective effect [194].

The meta-analysis by Kvaskoff et al. reported a slight association between endometriosis and breast cancer, with a 4% increased risk, consistent with findings by Gandini et al. However, breast cancer is a heterogeneous disease, with risk factors varying according to molecular subtypes and see underlying biological mechanisms [198]. To date, only one study has examined the association between endometriosis and specific breast cancer subtypes, reporting a 90% increased risk for ER+/PR− tumors in women with endometriosis, with no association observed for other subtypes [199]. This highlights the need for further investigations focusing on molecular subtypes, as already established for ovarian cancer.

Regarding thyroid cancer, an increased risk of 39% has been reported among women with endometriosis. However, this association may reflect a diagnostic bias, related to the higher likelihood of early detection among women with frequent access to healthcare services, as observed in the United States [200].

With respect to cutaneous melanoma, available data have not demonstrated a statistically significant association, in line with the findings of Gandini et al. Nevertheless, when the analysis was restricted to studies with low or moderate risk of bias, the association appeared stronger and statistically significant, suggesting the possible presence of effects masked by methodological bias and supporting the need for further high-quality studies [196].

Conversely, no evidence of an association has emerged between endometriosis and colorectal cancer, a finding confirmed by sensitivity analyses and consistent with previous literature. Similarly, no significant links have been identified with hematological, lung, gastric, hepatic, pancreatic, urinary, oral, or renal malignancies. A slight association has been observed with brain tumors; however, the limited number of available studies on these cancer sites warrants further research to clarify potential causal relationships [194].

For these reasons, clinical management of women with endometriosis should not be limited to symptom control alone, but should also include targeted surveillance aimed at early identification of potential oncological complications. Multidisciplinary collaboration among gynecologists, oncologists, and other specialists is therefore essential to ensure comprehensive, personalized, and evidence-based care [201].

11. ENDOMETRIOSIS AND MENOPAUSE

Endometriosis has long been regarded as an estrogen-dependent disease predominantly affecting women of reproductive age, with the assumption that lesions and symptoms regress after the onset of menopause. However, growing evidence indicates that endometriosis may persist, recur, or even present de novo during the peri- and postmenopausal periods, challenging this traditional view [202, 203]. Although postmenopausal endometriosis is relatively uncommon, with an estimated prevalence of up to 4%, its clinical relevance is considerable due to diagnostic difficulties, therapeutic challenges, and potential oncologic implications [204, 205].

The pathophysiology of endometriosis in menopause differs from that observed during reproductive life. A central unresolved issue concerns whether postmenopausal disease represents reactivation of pre-existing lesions or the development of new implants. This distinction is complicated by the high prevalence of undiagnosed or asymptomatic endometriosis during reproductive years [206]. Despite systemic hypoestrogenism, ectopic endometrial tissue retains the ability to produce estrogens locally

through autocrine and paracrine mechanisms. Overexpression of aromatase within endometriotic lesions, coupled with reduced activity of 17β-hydroxysteroid dehydrogenase type 2, results in sustained local E2 concentrations capable of supporting lesion survival and growth even after ovarian estrogen production has ceased [207, 208]

Additional estrogen sources may further contribute to disease persistence after menopause. Peripheral aromatization of androgens in adipose tissue represents a significant estrogen source, particularly in overweight and obese women [208]. Exogenous estrogen exposure, including hormone therapy and tamoxifen use, has been associated with reactivation of endometriotic lesions, especially when estrogen is administered without adequate progestogenic opposition [209]. Several observational studies suggest that estrogen-only hormone therapy is associated with a higher risk of recurrence compared with combined estrogen–progestogen regimens, supporting the protective role of progestins on ectopic endometrial tissue [210].

In 2022, the ESHRE guideline introduced a dedicated chapter on postmenopausal endometriosis, while simultaneously acknowledging that available evidence is scarce, of low quality, and insufficient to define the natural history of the disease after menopause (**Figure 11**) [211]. Clinically, endometriosis in menopause presents with heterogeneous and often nonspecific symptoms, frequently leading to delayed diagnosis. While many women experience symptom improvement after menopause, others report persistent or newly onset pelvic pain, sometimes occurring several years after the last menstrual period [212]. Clinical manifestations may include chronic pelvic pain, dyspareunia, bowel or urinary symptoms, and abnormal bleeding, depending on lesion location. Pain severity does not necessarily correlate with disease extent, reflecting the complex neuro-inflammatory mechanisms underlying endometriosis-associated pain [207]. Moreover, although overall quality of life may improve with age, menopausal women with a history of endometriosis, particularly those undergoing early surgical menopause, may experience persistent physical and psychological sequelae, including depressive symptoms and reduced sexual function [213, 214].

The relationship between endometriosis and menopause is further complicated by the impact of the disease and its treatment on ovarian function. Surgical management of ovarian endometriomas is consistently associated with a reduction in ovarian reserve, increasing the risk of premature or iatrogenic menopause [215]. In addition, the chronic inflammatory and oxidative microenvironment characteristic of endometriosis may independently contribute to follicular depletion. Consequently, women with endometriosis appear to have an increased likelihood of earlier menopause, with significant long-term consequences for bone, cardiovascular, and metabolic health [216].

Endometriosis and menopause			Chapter VI
	Clinicians should be aware that endometriosis, can still be active/symptomatic after menopause.		GDG STATEMENT
Treatment of endometriosis in postmenopausal women			
87	Clinicians may consider surgical treatment for postmenopausal women presenting with signs of endometriosis and/or pain to enable histological confirmation of the diagnosis of endometriosis.	⊕◯◯◯	Weak recommendation
88	The GDG recommends that clinicians acknowledge the uncertainty towards the risk of malignancy in postmenopausal women. If a pelvic mass is detected, the work-up and treatment should be performed according to national oncology guidelines.		GPP
89	For postmenopausal women with endometriosis-associated pain, clinicians may consider aromatase inhibitors as a treatment option especially if surgery is not feasible.	⊕◯◯◯	Weak recommendation
Menopausal symptoms in women with a history of endometriosis			
90	Clinicians may consider combined menopausal hormone therapy (MHT) for the treatment of postmenopausal symptoms in women (both after natural and surgical menopause) with a history of endometriosis.	⊕⊕◯◯	Weak recommendation
91	Clinicians should avoid prescribing estrogen-only regimens for the treatment of vasomotor symptoms in postmenopausal women with a history of endometriosis, as these regimens may be associated with a higher risk of malignant transformation.	⊕⊕◯◯	Strong recommendation
92	The GDG recommends that clinicians continue to treat women with a history of endometriosis after surgical menopause with combined estrogen-progestogen at least up to the age of natural menopause.		GPP
Menopause-related major health concerns in women with endometriosis			
	Clinicians should be aware that women with endometriosis who have undergone an early bilateral salpingo-oophorectomy as part of their treatment have an increased risk of diminished bone density, dementia, and cardiovascular disease. It is also important to note that women with endometriosis have an increased risk of cardiovascular disease, irrespective of whether they have had an early surgical menopause.		GDG STATEMENT

Figure 11. Recommendations on endometriosis in menopause as proposed by the ESHRE in the latest endometriosis guidelines (2022) [211].

One of the most clinically relevant aspects of postmenopausal endometriosis is the risk of malignant transformation. Although rare, with an estimated incidence of approximately 1%, malignant degeneration has been well documented, particularly in ovarian endometriosis [217]. Endometrioid and clear cell ovarian carcinomas are the histotypes most frequently associated with endometriosis. Identified risk factors include advanced age, long-standing disease, large endometriomas, and prolonged exposure to unopposed estrogen therapy [218]. Molecular studies have demonstrated shared genetic alterations between endometriotic lesions and associated malignancies, including mutations in ARID1A, PTEN, and components of the PI3K/AKT pathway, supporting a model of stepwise neoplastic transformation [217].

Beyond ovarian cancer, epidemiological studies have reported associations between endometriosis and other malignancies, including breast cancer and thyroid cancer, although causality remains uncertain and may be influenced by surveillance bias and shared risk factors. Conversely, an inverse association with cervical cancer has been described, likely reflecting increased healthcare utilization rather than a true protective effect [61].

Management of endometriosis in menopause remains challenging due to the paucity of high-quality evidence and the lack of specific guidelines. In symptomatic postmenopausal women, surgical excision of all visible disease is generally recommended, serving both diagnostic and therapeutic purposes while allowing histological exclusion of malignancy [219]. However, surgery may be technically demanding due to extensive fibrosis, deep infiltrating disease, and age-related comorbidities.

Medical therapy may be considered when surgery is contraindicated or symptoms persist. Progestins and the levonorgestrel-releasing intrauterine system represent potential options, although data in postmenopausal women are limited [7]. Aromatase inhibitors have emerged as a promising off-label

strategy by targeting extra-ovarian estrogen production and have shown efficacy in selected cases of postmenopausal endometriosis [220]. Nevertheless, their use is limited by hypoestrogenic side effects, particularly accelerated bone loss, necessitating careful patient selection and monitoring [221].

Treatment of menopausal symptoms in women with a history of endometriosis requires a careful balance between symptom relief and disease safety. Current evidence supports the use of continuous combined hormone therapy or tibolone rather than estrogen-only regimens in non-hysterectomized women [209]. Estrogen-only therapy has been associated with higher recurrence rates and increased oncologic risk and is therefore generally discouraged [222].

Finally, menopause represents a critical period for the emergence of long-term health consequences in women with endometriosis. Early menopause, chronic inflammation, and repeated hypoestrogenic treatments contribute to an increased risk of osteoporosis, cardiovascular disease, and metabolic disorders [61, 223]. These data highlight the need for a multidisciplinary approach to the care of menopausal women with endometriosis, integrating gynecological, oncologic, and cardiometabolic risk assessment in order to provide personalized, evidence-based management.

12. LINKING ENDOMETRIOSIS AND MENOPAUSE: RATIONALE FOR THE PRESENT STUDY

As explained above, endometriosis has been considered a disease confined to the reproductive years, driven primarily by ovarian estrogen production. The natural decline in circulating estrogens after menopause has therefore long been assumed to induce regression or complete resolution of the disease. However, increasing evidence suggests that this paradigm is overly simplistic. While clinical symptoms may attenuate after menopause, structural and biological sequelae of endometriosis frequently persist and, in selected cases, may remain clinically relevant or even progressive.

Several mechanisms may account for the persistence of endometriotic lesions beyond menopause. First, fibrotic remodeling and chronic inflammatory changes acquired during reproductive life are unlikely to regress once established, resulting in residual nodules that may remain detectable on imaging even in the absence of hormonal stimulation. Second, extra-ovarian estrogen production—particularly via aromatase activity in adipose tissue, skin, and endometriotic implants themselves—may sustain low-level local estrogenic stimulation despite systemic hypoestrogenism. Third, postmenopausal hormone therapy, whether systemic or local, may further modulate lesion activity in susceptible individuals. These mechanisms help explain why endometriosis-related findings may persist, evolve, or occasionally become clinically relevant even years after menopause.

From a clinical standpoint, this phenomenon raises important diagnostic and prognostic challenges. In postmenopausal women, endometriotic lesions may present with atypical morphology, reduced inflammatory activity, or fibrotic transformation, often mimicking malignant disease or remaining clinically silent. Consequently, the distinction between inactive fibrotic remnants, hormonally active disease, and neoplastic transformation becomes increasingly complex. This is particularly relevant given that certain ovarian and extra-ovarian malignancies may arise in association with endometriosis or share overlapping imaging features.

Despite these considerations, the literature addressing endometriosis in postmenopausal women remains remarkably scarce. Most available data derive from isolated case reports, small surgical series, or retrospective observations, with limited systematic imaging-based evaluation. As a result, the true prevalence, anatomical distribution, and ultrasonographic phenotype of postmenopausal endometriosis remain poorly defined. Moreover, little is known about the relationship between residual lesions and prior symptomatology, hormonal exposure, or long-term disease evolution.

In this context, the following study, presented in the current thesis, aims to fill a critical knowledge gap by systematically characterizing ultrasound findings suggestive of endometriosis in a large cohort of postmenopausal women undergoing routine gynecological evaluation. By correlating imaging features with clinical history and symptomatology, this work seeks to clarify whether postmenopausal

endometriosis represents a quiescent footprint of past disease, a hormonally modulated condition, or a potential diagnostic pitfall with oncologic implications. This approach may contribute to refining diagnostic strategies, improving risk stratification, and guiding appropriate surveillance in this understudied population.

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Title: Prevalence, ultrasound characterization, and oncologic differential diagnosis of endometriosis in postmenopausal women undergoing routine gynecological examination

ABSTRACT

Objective

To systematically assess the prevalence, ultrasonographic characteristics, and clinical correlates of findings suggestive of deep endometriosis (DE) in postmenopausal women undergoing routine gynecological evaluation.

Methods

This prospective, observational study (NCT07503938) included consecutive postmenopausal women attending a regional gynecology outpatient clinic for routine examination over 12 months. All participants underwent a transvaginal ultrasound performed by an expert operator according to the standardized International Deep Endometriosis Analysis (IDEA) group criteria. Ultrasonographic findings suggestive of DE and/or endometrioma-like cysts were recorded and characterized. Clinical data were collected using a structured questionnaire. Univariable and multivariable logistic regression analyses were performed to identify factors independently associated with posterior compartment hypoechoic nodules.

Results

Four hundred ninety-two postmenopausal women were included (mean age 60.2 ± 6.1 years; median time since menopause 8.0 years). Ultrasound findings suggestive of endometriosis were identified in 40 women (8.1%; 95% CI 5.9–10.9%), including posterior compartment hypoechoic nodules in 36 (7.3%). Intestinal nodules (n=21; 4.3%) often displayed a thin, hypoechoic morphology with regular margins, minimal or absent Doppler vascularization, and rare submucosal layer involvement. The

prevalence of DE nodules decreased progressively with increasing time since menopause (13.9% within ≤5 years vs 4.3% >10 years; p for trend = 0.02). In multivariable analysis, being within five years of menopause was independently associated with posterior hypoechoic nodules (adjusted OR 3.31, 95% CI 1.38–7.94), as were a history of dysmenorrhea (adjusted OR 2.26, 95% CI 1.08–4.74) and chronic pelvic pain (adjusted OR 2.37, 95% CI 1.18–4.87) during reproductive life. No independent association was observed with previous infertility, current pelvic, sexual, or bowel symptoms, nor with systemic hormone replacement therapy. Six ovarian cysts suggestive of endometriomas were identified (1,2%, 95%CI, 0.45%-2.64%, frequently (83.3%) displaying atypical sonographic features (multilocularity, heterogeneous internal echoes, focal papillary excrescences, or localized wall thickening). Importantly, one rectal hypoechoic lesion with marked vascularization and transmural involvement was diagnosed as rectal adenocarcinoma, and one surgically treated atypical endometrioma-like cyst was a FIGO stage I serous borderline ovarian tumor.

Conclusions

Ultrasound findings suggestive of DE may be detected in postmenopausal women and are strongly associated with early postmenopausal timing and a history of reproductive-age pain, rather than with current symptoms or hormonal exposure. These lesions most likely represent quiescent fibrotic sequelae of previously unrecognized disease. Given the potential for malignant mimics in clinical findings and endometriosis-associated adnexal neoplasia, expert ultrasound assessment and appropriate triage of atypical or vascular lesions are essential in this population.

INTRODUCTION

Endometriosis is a chronic, estrogen-dependent disorder characterized by the presence of endometrial-like glands and stroma outside the uterine cavity, affecting an estimated 6–10% of reproductive-age women [1]. Although its pathogenesis is multifactorial—encompassing retrograde menstruation, hormonal dysregulation, immune dysfunction, and genetic susceptibility—estrogen is the principal driver of ectopic endometrial proliferation and inflammatory activity [2]. During reproductive years, systemic ovarian estrogen sustains lesion activity and symptoms such as pelvic pain, dysmenorrhea, dyspareunia, and infertility [3]. Disease most commonly involves the ovaries, uterosacral ligaments, and rectovaginal space, but can extend to the urinary tract and diaphragm [4]. In this setting, transvaginal ultrasound (TVS) has become the first-line modality for detection and mapping of ovarian and deep endometriosis (DE), and the standardized IDEA (International Deep Endometriosis Analysis group) approach has demonstrated high diagnostic performance in symptomatic premenopausal women [5, 6].

Because of its hormonal dependence, endometriosis has long been regarded as a condition confined to the reproductive years. Menopause, characterized by ovarian senescence and declining systemic estrogen levels, is typically associated with symptom remission, and many previously affected women experience a substantial reduction in pain and discontinuation of hormonal treatment [2]. However, this view may be overly simplistic: morphological alterations driven by chronic inflammation and fibrosis are unlikely to regress immediately in parallel with hormonal withdrawal and may persist for years as structural residues of the disease, potentially causing pelvic pain even in the absence of a cyclical menstrual pattern. In addition, localized estrogen biosynthesis within endometriotic implants, extragonadal estrogen production in adipose tissue and exogenous hormonal exposure through hormone replacement therapy (HRT) have been proposed as mechanisms that could theoretically sustain some degree of postmenopausal disease activity and, albeit rarely, contribute to malignant transformation, although their true clinical impact remains uncertain and is still a matter of debate [7].

In 2022, the ESHRE guideline introduced a dedicated chapter on postmenopausal endometriosis, while simultaneously acknowledging that available evidence is scarce, of low quality, and insufficient to define the natural history of the disease after menopause [8]. Most of what is known derives from case reports, small surgical series, or incidental autopsy findings, and population-based estimates of a 2–4% prevalence likely underestimate the true burden, as many lesions remain clinically silent [9-11]. Furthermore, women currently in their sixth or seventh decade lived their reproductive years in an era of limited awareness and lower diagnostic accuracy—particularly before widespread access to high-resolution TVS—raising the possibility that a substantial proportion of postmenopausal findings may represent long-standing, previously unrecognized sequelae of endometriosis.

Despite this, the sonographic appearance of endometriosis in postmenopausal women has never been systematically described, even by operators with extensive expertise in endometriosis imaging. Consequently, we lack robust data on the prevalence, anatomical distribution, and morphological characteristics of ultrasound findings suggestive of endometriosis in this population. The aim of this study was therefore to describe, in a large cohort of postmenopausal women undergoing routine gynecological examination, the prevalence and sonographic phenotype of hypoechoic findings suggestive of previous endometriosis, and to explore their clinical correlates.

MATERIALS AND METHODS

Study design and population

This was a prospective, observational study that included all postmenopausal women aged 50 years or older who consecutively attended two regional gynecology outpatient clinics for routine examinations over a 12-month period (ASL-4 Liguria, Metropolitan Area of Genoa, Italy, and IRRCS Ospedale Policlinico San Martino, Genoa, Italy) between June 2023 and June 2025. Menopause was defined as at least 12 consecutive months of spontaneous amenorrhea not attributable to pregnancy, lactation, medical therapy, or other pathological causes. Women with a previous radiological

(including ultrasonographic) and/or surgical diagnosis of endometriosis, a history of hysterectomy and/or bilateral oophorectomy (any route), or active pelvic malignancy were excluded.

TVS was not performed, and participants were excluded from the analysis, when the examination was not feasible or not interpretable for predefined technical reasons, including inability to tolerate probe insertion (e.g., severe introital stenosis, vaginismus, or never sexually active/virgin women. Current or prior use of HRT was recorded but was not considered an exclusion criterion.

Clinical assessment and data collection

At the gynecological visit, each participant completed a structured questionnaire specifically designed for this study. The questionnaire collected detailed demographic, reproductive, and clinical information, including age, body mass index (BMI), parity, smoking status, medical comorbidities, and time since menopause.

Gynecological history was recorded with particular attention to pain-related symptoms during reproductive life, including dysmenorrhea, chronic pelvic pain, dyspareunia, and dischezia, as well as prior pelvic or abdominal surgery. A history of infertility was recorded when women reported ≥12 months of unsuccessful conception attempts and/or a previous clinical diagnosis of infertility and/or the use of medically assisted reproduction.

Information on menopausal status and hormonal exposure was collected in detail, including current or previous use of HRT, also reporting the type of regimen (combined estrogen–progestin, tibolone, or other).

Current symptoms were assessed at the time of the visit using an 11-point numeric rating scale (NRS; 0 = no pain, 10 = worst imaginable pain) for pelvic pain, deep and superficial dyspareunia, and dischezia. Clinically relevant pain was prespecified as an NRS score ≥3. Participants were also asked about gastrointestinal symptoms, including changes in bowel habits, abdominal bloating, and unexplained rectal bleeding. Lower urinary tract symptoms (LUTS) were systematically recorded as

well, including urinary frequency, urgency, dysuria, and nocturia, as well as any history of recurrent urinary tract infections or macroscopic hematuria.

For each participant, questionnaire responses and relevant clinical information retrieved from medical records (including comorbidities, medications, and previous imaging or surgical reports) were coded using predefined categories and entered into a dedicated electronic database. Data entry procedures incorporated internal consistency checks to minimize transcription errors and ensure uniformity across variables.

Ultrasonographic protocol

All participants underwent a standardized TVS examination performed with a 5–9 MHz transvaginal transducer. All examinations were conducted by a single operator with extensive expertise in TVS and endometriosis imaging, ensuring consistency and minimization of inter-observer variability.

In postmenopausal women, the baseline scan included systematic evaluation of uterine size and morphology, endometrial thickness and echogenicity, myometrial texture, adnexal structures and ovarian remnants (when visualized), and exclusion of pelvic masses or free fluid. The bladder, ureters, and rectosigmoid region were also routinely inspected to exclude non-gynecologic pelvic pathology.

The examination incorporated the first three steps of the IDEA consensus for the identification of indirect signs of DE [5]. First, the uterus and adnexa were evaluated for ultrasonographic direct and indirect features of adenomyosis—recorded according to the revised MUSA criteria [12] —as well as for the presence of endometriomas, consisting in unilocular cysts with homogeneous ground-glass echogenicity. In line with age-related changes described in the literature, endometriomas in older women may more frequently display atypical sonographic features (such as solid components, papillary projections, or heterogeneous internal echoes); these aspects were therefore carefully sought and systematically documented in detail [13].

Second, soft markers of pelvic adhesions and possible DE were assessed. Ovarian mobility and tenderness were evaluated by exerting gentle pressure between the ovary and uterus: reduced or

absent gliding suggested adhesions, including the presence of “kissing ovaries.” The distal third of both ureters was identified and scrutinized for dilatation, as previously described [14], complementing this evaluation by abdominal ultrasonography to assess for hydronephrosis through inspection of calyceal dilatation, renal pelvis configuration, and cortical thickness.

Third, the status of the pouch of Douglas was investigated using the posterior sliding sign. A negative sliding sign was defined as the absence of physiological movement between the rectum and the posterior uterine wall or cervix during probe-induced mobilization, suggesting potential adhesion or obliteration of the pouch of Douglas related to posterior compartment DE [15]. Similarly, the anterior sliding sign was assessed to identify reduced mobility between the bladder wall and the anterior uterine surface, indicative of adhesions at the vesicouterine fold [16].

Following this preliminary assessment, a systematic evaluation of pelvic compartments (IDEA step 4) was carried out. The posterior compartment, including the rectosigmoid, uterosacral ligaments, rectovaginal septum, and posterior vaginal fornix, was carefully examined for hypoechoic nodules or focal thickening. Normal rectal wall layers can be visualized on TVS: the anterior rectal serosa is seen as a thin hyperechoic line; the muscularis propria is hypoechoic, with the longitudinal smooth muscle and circular smooth muscle separated by a faint, thin hyperechoic line; the submucosa is hyperechogenic; and the mucosa is hypoechoic. Bowel DE usually appears on TVS as a thickening of the hypoechoic muscularis propria or as hypoechoic nodules, with or without hyperechoic foci with blurred margins. Rectovaginal lesions were identified as nodules located below the peritoneal reflection along the lower margin of the posterior cervix, whereas vaginal involvement manifested as thickening or distortion of the posterior fornix. The uterosacral ligaments, representing the most accessible component of the posterior parametrium on TVS, were inspected in transverse and longitudinal planes for hypoechoic thickening or focal nodularity. The other parametrial regions were evaluated according to recent standardized evidence [17, 18].

To obtain a detailed morphologic description of DE in this postmenopausal population, each suspected DE lesion was systematically characterized using a predefined set of sonographic features.

For every nodule we recorded maximum thickness, margin regularity, internal echotexture, presence of hyperechoic foci, relationship with adjacent structures, and, in the case of intestinal lesions, the presence or absence of apparent infiltration of the intestinal layers, as previously reported [19]. This standardized morphologic assessment allowed us to describe how DE nodules appeared in this cohort, including thin hypoechoic lesions with regular margins as well as more complex or atypical presentations. Lesions extending across more than one anatomical structure were classified as separate sites to maintain consistency in anatomical mapping. All examinations and representative images were digitally archived for subsequent review and quality control.

Statistical analysis

The prevalence of ultrasound findings suggestive of endometriosis was calculated as the proportion of women presenting with at least one finding suggestive of DE and/or an endometrioma-like ovarian cyst, with exact 95% confidence intervals (Clopper–Pearson method). Prevalence estimates and regression analyses were performed after excluding women in whom a suspected endometriosis-related lesion was subsequently reclassified as malignancy at histology.

Associations between ultrasound findings and clinical variables were first explored using univariable logistic regression. A prespecified multivariable logistic regression model was then fitted to identify independent predictors of posterior compartment hypoechoic nodular thickenings, including age category, time since menopause, reproductive-age pain history, infertility history, HRT exposure, and selected current symptom domains assessed at the time of visit. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs), and a two-sided p value <0.05 was considered statistically significant. Multicollinearity was assessed using the variance inflation factor (VIF), with values <2 considered acceptable.

All analyses were performed using SPSS Statistics v25.0 (IBM Corp., Armonk, NY, USA).

Ethical procedures

The study protocol was approved by the local ethics committee (N. CET - Liguria: 412/2024 - DB id 14211; last vers. approval 02/2025) and conducted in accordance with the Declaration of Helsinki. This study was registered in ClinicalTrials.gov (NCT07503938). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology checklist for case-control study. All data were anonymized before analysis to ensure patient confidentiality.

RESULTS

Overall population characteristics

Four hundred ninety-two postmenopausal women were included in the analysis. Mean age was 60.2 ± 6.1 years, and the median time since menopause was 8.0 years (IQR 4.3–12.9). A larger proportion of patients reported a history of dysmenorrhea (n=165; 33.5%) or chronic pelvic pain (n=125; 25.4%) during reproductive life.

At the time of assessment, current pelvic pain was reported by 70 women (14.2%). Deep dyspareunia and superficial dyspareunia were reported by 55 (11.2%) and 87 (17.7%) women, respectively. Vaginal dryness was reported by 213 women (43.3%). Regarding postmenopausal hormonal exposure, current systemic HRT was reported by 55 women (11.2%), and past systemic HRT by 22 (4.5%) (overall systemic HRT exposure: n=76 women; 15.4%). The use of local vaginal estrogen or dehydroepiandrosterone (DHEA) preparations only was reported by 56 women (11.4%). Additional demographic and clinical characteristics of the study population are reported in **Table 1** and **Supplementary Table 1**.

Table 1. Demographic characteristics of the study population

Characteristic	Value
Age, years	
Mean ± SD	60.2 ± 6.1
Range	47–81
Age > 65 years, n (%)	104 (21.2)
Body mass index (BMI), kg/m²	
Mean ± SD	24.4 ± 6.2
BMI < 25, n (%)	291 (59.1)
BMI 25–29.9, n (%)	128 (26.0)
BMI ≥ 30, n (%)	73 (14.9)
Time since menopause, years	
Median (IQR)	7 (2–12)
≤ 5 years, n (%)	151 (36.6)
6–10 years, n (%)	154 (30.5)
> 10 years, n (%)	187 (32.9)
Reproductive history	
Nulliparous women, n (%)	82 (16.7)
Parous women, n (%)	410 (83.3)

Characteristic	Value
Parity ≥ 2, n (%)	280 (56.9)
History of infertility, n (%)	90 (18.3)
Gynecological history during reproductive age	
History of dysmenorrhea, n (%)	165 (33.5)
History of chronic pelvic pain, n (%)	125 (25.4)
Previous abdominal surgery (any), n (%)	225 (45.7)
Current symptoms at time of visit	
Pelvic pain, n (%)	70 (14.2)
Deep dyspareunia, n (%)	55 (11.2)
Superficial dyspareunia, n (%)	87 (17.7)
Dyschezia, n (%)	37 (7.5)
Abdominal bloating, n (%)	103 (20.9)
Constipation, n (%)	137 (27.8)
Diarrhea, n (%)	30 (6.1)
LUTS (urinary frequency, urgency), n (%)	116 (23.4)
Vaginal dryness, n (%)	213 (43.3)
Hormonal exposure after menopause	
Systemic hormone replacement therapy (current or past), n (%)	76 (15.4)
Combined estrogen–progestin regimen, n (%)	44 (8.9)
Tibolone or other regimens, n (%)	32 (6.5)
Local vaginal estrogen only (current or past), n (%)	56 (11.3)
Never used hormone therapy after menopause, n (%)	360 (73.3)

Characteristic	Value
Medical comorbidities	
Hypertension, n (%)	165 (33.5)
Diabetes mellitus, n (%)	47 (9.6)
Thyroid disease, n (%)	61 (12.4)
Other autoimmune disorders, n (%)	26 (5.3)
Lifestyle factors	
Current or former smoking, n (%)	148 (30.1)

Ultrasonographic findings

Hypoechoic nodular thickenings in the posterior compartment and/or adnexal cystic formations suggestive of endometriosis were identified in 40 women (8.1%; 95% CI 5.9–10.9%). Hypoechoic nodulations in the posterior compartment, suggestive of DE, were observed in 36 women (7.3%; 95% CI 5.2–10.0%; **Figures 1 and 2**). Their anatomical distribution of nodules included the lower or upper rectum (n = 15), the rectosigmoid junction or sigmoid colon (n = 6), the uterosacral ligaments and uterine torus (n = 19), and the rectovaginal septum or posterior vaginal fornix (n = 4); seven women (7.1%) harbored more than one lesion, each classified individually according to predefined anatomical criteria. A reduced or absent posterior sliding sign was observed in 75 women (15.2%). Among these, 20 patients (26.7%) also had at least one posterior hypoechoic nodule.

From a morphological perspective, most intestinal nodules displayed a plaque-like hypoechoic pattern (mean largest diameter 14 ± 6.8 mm). A maximum thickness < 7 mm was recorded in 18 of 21 lesions (85.7%), and margins were judged regular in 17 of them (81.0%). In 16 nodules (76.2%), there was no sonographic evidence of submucosal layer involvement, whereas the lesion–tissue

interface appeared indistinct, with blurred margins showing a gradual, subtly hypoechoic transition into the surrounding tissue in 14 lesions (66.7%) (**Figure 1**).

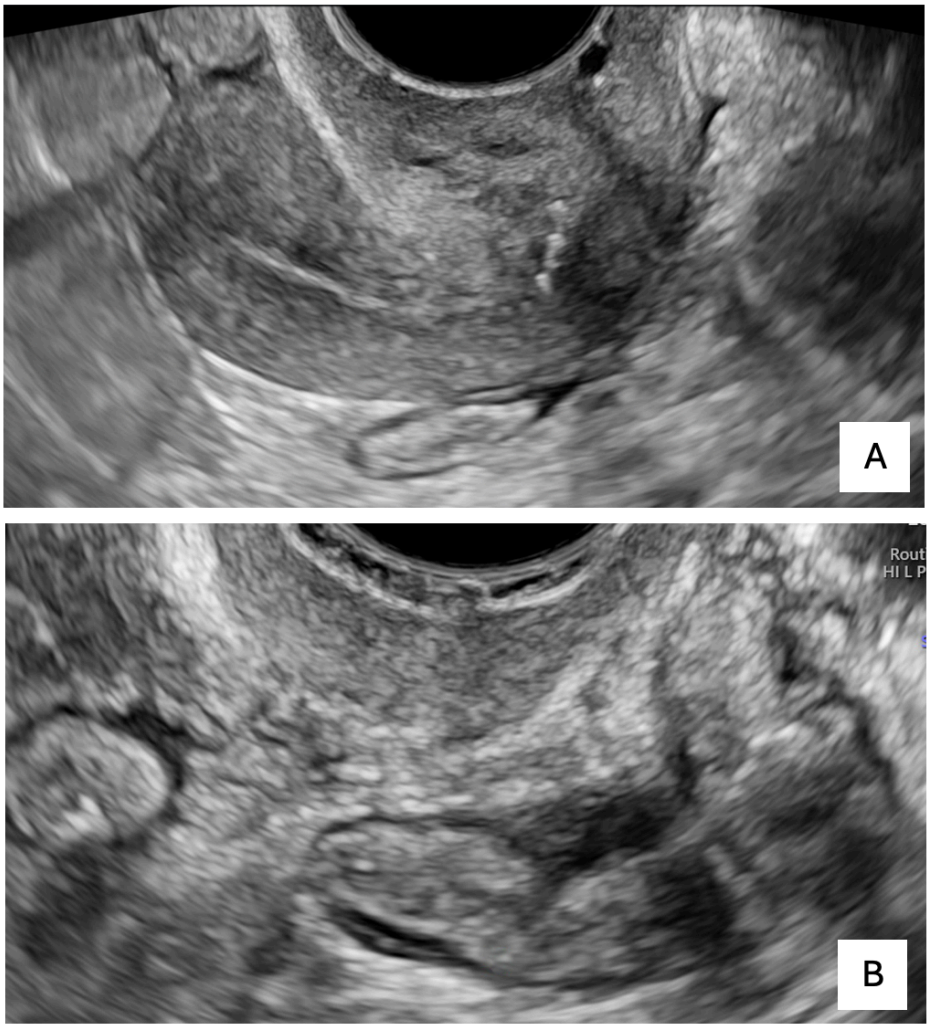

Figure 1. (A) The uterus shows features consistent with menopausal involution, with a thin endometrium (endometrial thickness 1.5 mm) and mild asymmetry between the anterior and posterior uterine walls. (B) A plaque-like hypoechoic lesion is visible, with a flattened morphology and indistinct, subtly hypoechoic margins at the interface with the surrounding tissues. The lesion is < 10 mm deep, with no sonographic evidence of submucosal or mucosal involvement.

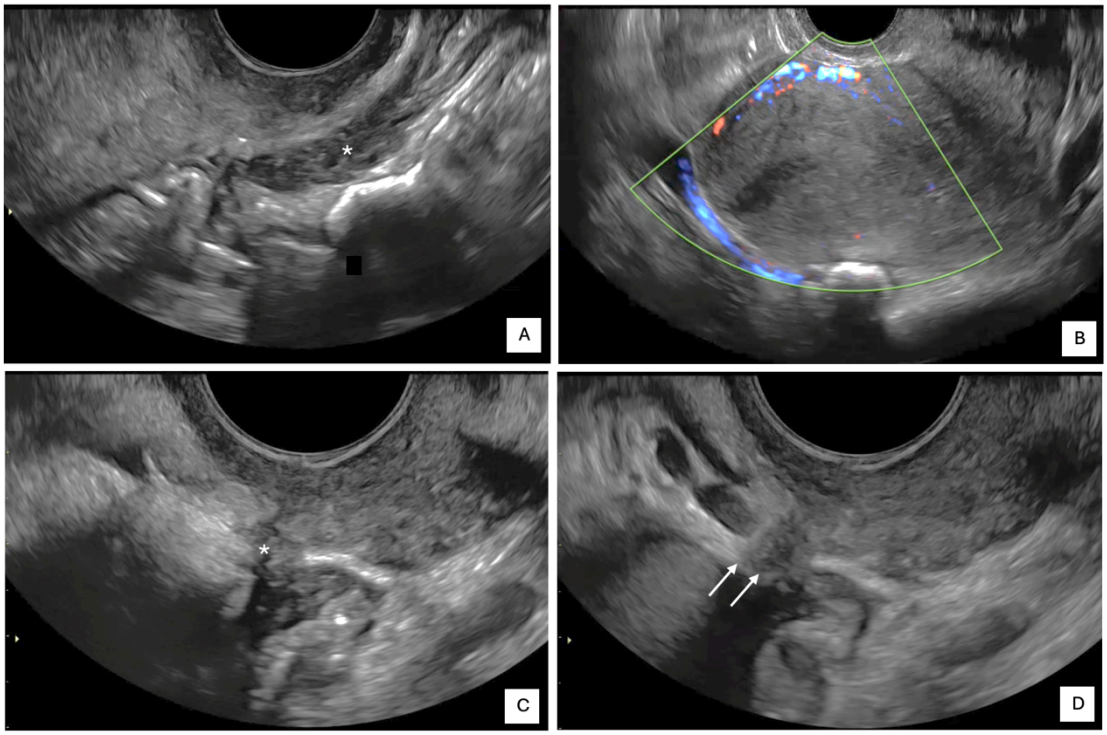

Figure 2. (A) A hypoechoic lesion (asterisk), showing more regular margins and focal thickening of the anterior rectal wall; a maximum thickness of 6 mm was recorded, with no sonographic evidence of (sub)mucosal layer involvement. (B) Concomitant left ovarian cyst suggestive of an endometrioma with atypical features, characterized by isoechoic, non-uniform internal echoes, deviating from the typical "ground glass" appearance, and without relevant intralesional vascularisation on Doppler assessment. (C) Another hypoechoic lesion is visible in the posterior compartment, with a flattened morphology and indistinct, subtly hypoechoic margins, involving the left uterosacral ligament (*) and extending into the left posterolateral parametrium. The lesion shows a tapering configuration, consistent with fibrotic extension. (D) Cranial extension of the lesion reaches the lateral parametrial plane (arrows) up to the uterine vessels, which appear not infiltrated. The adjacent ovarian cyst appears fixed, supporting the presence of adhesions within the posterior compartment.

One intestinal lesion showed pronounced vascularization on color Doppler, a maximum thickness > 10 mm, massive involvement of the submucosal and mucosal layers, and clinically relevant rectal bleeding. Colonoscopy in this case revealed a rectal adenocarcinoma, which was treated with neoadjuvant radiotherapy followed by surgical resection.

Ultrasonographic features suggestive of adenomyosis were identified in 32 women (6.5%). The most common direct sign was the presence of hyperechoic myometrial islands (n=25; 78.1%). Among indirect signs, asymmetry between the anterior and posterior uterine walls was observed in 12 women (37.5%), while an interrupted junctional zone was documented in 10 (31.3%).

Adnexal assessment revealed endometrioma-like cystic formations in six women (1.2%). One cyst exhibited the classic unilocular "ground-glass" appearance and was managed conservatively. The remaining five cysts showed atypical sonographic features, including multilocularity, heterogeneous internal echoes, focal papillary excrescences, or localized wall thickening (**Figures 3 and 4**).

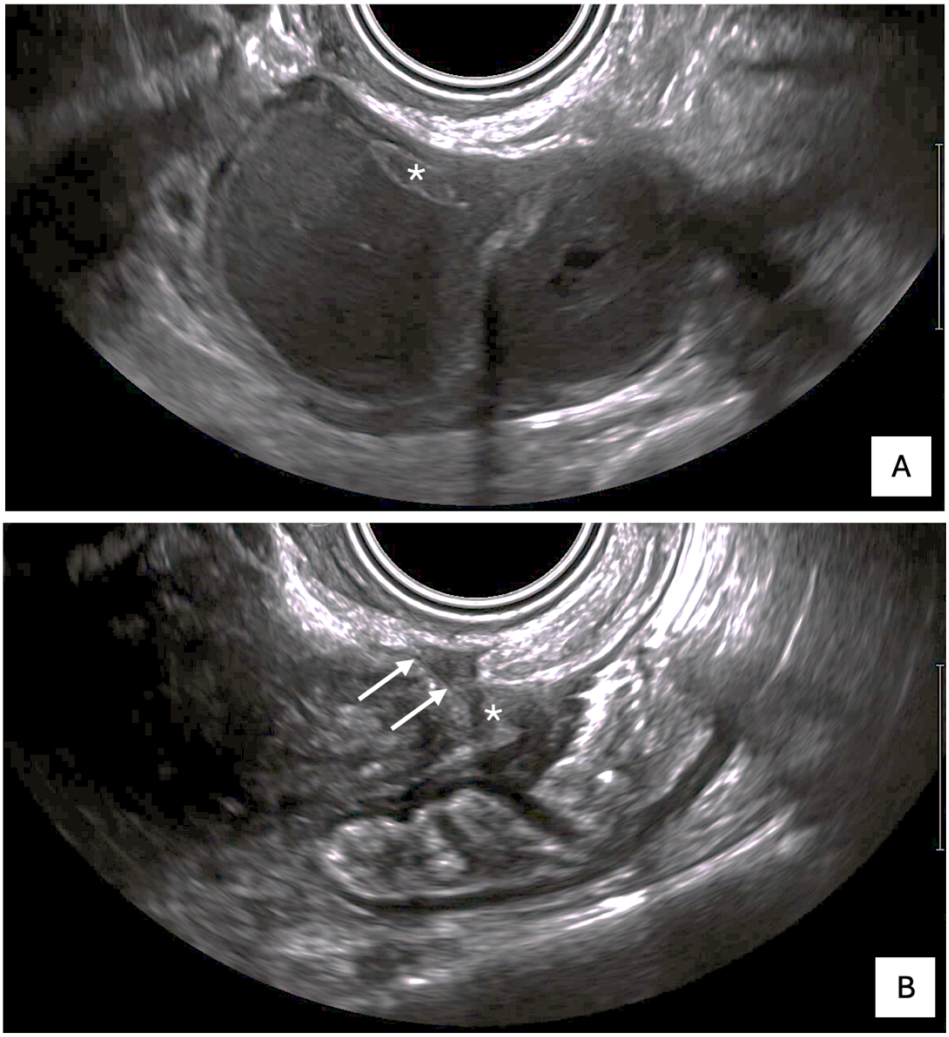

Figure 3. (A) Bilocular endometrioma-like cyst (37x32 mm), characterized by homogeneous low-level internal echoes and the presence of an avascular intracystic hyperechogenic concretion (*). (B) Orthogonal

scan of the posterior compartment showing a low-profile, plaque-like hypoechoic lesion (23x5 mm) with flattened morphology and indistinct, subtly hypoechoic margins. The lesion extends along the left uterosacral ligament (*) and tapers into left right posterior parametrium (arrows). It appears non-bulky, with preserved layered anatomy of the adjacent bowel wall and no sonographic evidence of submucosal or mucosal involvement.

Serum CA125 levels were measured in three of these cases and were within the normal range in two women, while a modest elevation above the conventional cut-off was documented in one patient (40.4 U/mL). In view of postmenopausal status, atypical morphology, and, in one case, CA125 elevation, three women were referred for surgical management. Histopathological examination confirmed benign endometriosis-related pathology in two cases, whereas one lesion was diagnosed as a FIGO stage I serous borderline tumor confined to the ovary (**Figure 4a**).

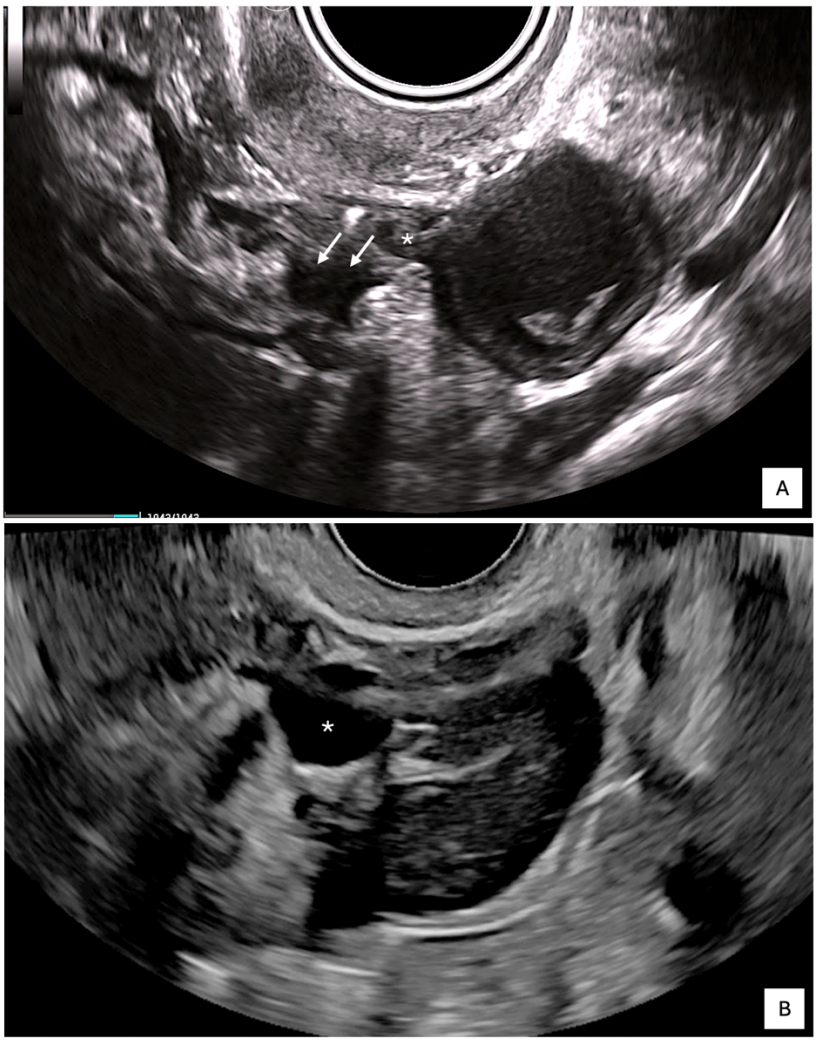

Figure 4. (A) An atypical ovarian endometrioma-like cyst is visible, characterized by homogeneous low-level internal echoes and an intracystic echogenic concretion, with detectable mild vascularization on Doppler assessment. The cyst appears adherent to the left uterosacral ligament, where a deep endometriotic implant is identified (*). The implant shows a flattened morphology and indistinct, subtly hypoechoic margins, consistent with fibrotic involvement of the left posterior parametrium, extending to the anterior wall of the upper rectum (arrows). The cyst had been persistently present for 5 years and was associated with a CA125 level of 40.4 U/mL, prompting surgical management; histopathology ultimately confirmed a serous borderline tumor confined to the ovary (FIGO stage I).

(B) Another endometrioma-like cyst, with atypical features, showing a mixed internal echotexture with a partially anechoic component (*) and non-uniform low-level echoes, deviating from the typical "ground glass" appearance. The cyst content appears mildly heterogeneous and layered, without internal vascularisation on Doppler assessment.

Other incidental gynecological findings at ultrasound included uterine fibroids (n = 158; 32.2%), congenital uterine malformations (n = 8; 1.7%), and simple ovarian cysts <3 cm (n = 23; 4.7%), three of which (0.7% overall) required surgical management due to atypical morphology in accordance with postmenopausal risk stratification.

Supplementary Table S1. Baseline characteristics of women with and without posterior hypoechoic nodules in postmenopausal women

Variable	Posterior nodules (n = 36)	No nodules (n = 456)	p value
Age, years	57.1 ± 4.6	60.5 ± 6.1	<0.001
Age ≥65 years, n (%)	3 (8.3%)	101 (22.1%)	0.051
Time since menopause, n (%)			<0.001†

Variable	Posterior nodules (n = 36)	No nodules (n = 456)	p value
≤5 years	21 (58.3%)	130 (28.5%)	
6–10 years	7 (19.4%)	147 (32.2%)	
>10 years	8 (22.2%)	179 (39.3%)	
BMI, kg/m²	24.2 ± 6.4	24.4 ± 6.3	0.888
History during reproductive life			
Dysmenorrhea, n (%)	20 (55.6%)	145 (31.8%)	0.006
Chronic pelvic pain, n (%)	16 (44.4%)	109 (23.9%)	0.033
Dysmenorrhea and/or CPP, n (%)	26 (72.2%)	208 (45.6%)	0.004
History of infertility, n (%)	9 (25.0%)	63 (13.8%)	0.113
Previous abdominal surgery (any#)	21 (58.3%)	204 (44.7%)	0.121
Current symptoms			
Pelvic pain, n (%)	8 (22.2%)	62 (13.6%)	0.239
Deep dyspareunia, n (%)	6 (16.7%)	49 (10.7%)	0.418
Superficial dyspareunia, n (%)	7 (19.4%)	70 (15.4%)	0.684
Abdominal bloating, n (%)	9 (25.0%)	115 (25.2%)	0.984
Constipation, n (%)	7 (19.4%)	79 (17.3%)	0.930
Diarrhea, n (%)	1 (2.8%)	21 (4.6%)	0.925‡
Intestinal symptoms (any), n (%)	11 (30.6%)	141 (30.9%)	0.978
LUTS, n (%)	12 (33.3%)	166 (36.4%)	0.841
Vaginal dryness, n (%)	18 (50.0%)	195 (42.8%)	0.504
Hormonal exposure after menopause			
Systemic HRT (past or current), n (%)	9 (25.0%)	67 (14.7%)	0.159

Variable	Posterior nodules (n = 36)	No nodules (n = 456)	p value
Local estrogen/DHEA only, n (%)	3 (8.3%)	53 (11.6%)	0.785

† Overall association across categories (χ^2); p for trend across ordered categories = 0.001.

‡ Fisher's exact test. # excluding for diagnosing/treating endometriosis

BMI: body mass index; DHEA: dehydroepiandrosterone; LUTS: lower urinary tract symptoms; HRT: hormone replacement therapy

Exploratory analyses

When the population was stratified according to time since menopause, the prevalence of hypoechoic nodular thickenings progressively decreased across categories, from 13.9% in women within five years of menopause to 4.5% in those 6–10 years from menopause and 4.3% in women more than ten years beyond menopause (p for trend = 0.02).

In univariate logistic regression analysis (**Table 2**), a history of dysmenorrhea (OR 2.68, 95% CI 1.35–5.33; p = 0.005) and chronic pelvic pain (OR 2.55, 95% CI 1.28–5.09; p = 0.008) during reproductive life were significantly associated with the presence of posterior hypoechoic nodules. Women within five years from menopause onset showed a markedly increased odds of nodular findings compared with those more than ten years beyond menopause (OR 3.61, 95% CI 1.55–8.42; p = 0.003). A history of infertility was not significantly associated with posterior nodular findings (OR 2.08, 95% CI 0.93–4.63; p = 0.073). Furthermore, no significant associations were observed with current pelvic, sexual, or bowel symptoms, systemic HRT, or local estrogen use (all p > 0.05).

Table 2. Univariable logistic regression analyses of factors associated with posterior compartment hypoechoic nodules in postmenopausal women

Predictor	Unadjusted OR (95% CI)	p
Age ≥65 vs <65 yr	0.32 (0.10–1.06)	0.063
Time since menopause: 6–10 vs >10 yr	1.07 (0.38–3.01)	0.905
Time since menopause: ≤5 vs >10 yr	3.61 (1.55–8.42)	0.003
BMI (kg/m²)	1.00 (0.94–1.05)	0.886
History of infertility	2.08 (0.93–4.63)	0.073
Previous abdominal surgery (any†)	1.14 (0.56–2.33)	0.71
History of dysmenorrhea	2.68 (1.35–5.33)	0.005
History of chronic pelvic pain	2.55 (1.28–5.09)	0.008
Any systemic HRT (past or current)	1.94 (0.87–4.30)	0.105
Local estrogen/DHEA only	0.69 (0.20–2.33)	0.552
Current pelvic pain	1.82 (0.79–4.16)	0.159
Current deep dyspareunia	1.66 (0.66–4.19)	0.282
Current dyschezia	2.14 (0.78–5.87)	0.141

Outcome: presence of ≥1 posterior compartment hypoechoic nodule (yes/no)

† excluding for diagnosing/treating endometriosis

BMI: body mass index; HRT: hormone replacement therapy; DHEA: dehydroepiandrosterone; yr: years

In the multivariable logistic regression model (**Table 3**), being within five years from menopause remained independently associated with posterior hypoechoic nodules (adjusted OR 3.31, 95% CI 1.38–7.94; p = 0.007). A history of dysmenorrhea (adjusted OR 2.26, 95% CI 1.08–4.74; p = 0.031) and chronic pelvic pain (adjusted OR 2.37, 95% CI 1.18–4.87; p = 0.022) during reproductive life also retained independent significance. In contrast, a history of infertility, exposure to HRT, and the

presence of current pelvic, sexual, or intestinal symptoms were not independently associated with nodular ultrasound findings (all $p > 0.05$).

In additional exploratory analyses, no demographic, reproductive, clinical, or hormonal variables were significantly associated with the presence of endometrioma-like cystic formations or adenomyosis features, and no independent predictors were identified in either univariate or multivariable logistic regression models (all $p > 0.05$).

Table 3. Multivariable logistic regression analyses of factors associated with posterior compartment hypoechoic nodules in postmenopausal women

Predictor	Adjusted OR (95% CI)	p
Time since menopause: ≤5 vs >10 yr	3.31 (1.38–7.94)	0.007
Time since menopause: 6–10 vs >10 yr	0.90 (0.31–2.64)	0.853
History of dysmenorrhea	2.26 (1.08–4.74)	0.031
History of chronic pelvic pain	2.37 (1.18–4.87)	0.022
History of infertility	2.04 (0.87–4.80)	0.101
Any systemic HRT (past or current)	2.06 (0.88–4.80)	0.095
Current pelvic pain	1.37 (0.56–3.38)	0.491
Current deep dyspareunia	2.11 (0.77–5.78)	0.146
Current dyschezia	2.32 (0.79–6.80)	0.126

HRT: hormone replacement therapy; yr: years

DISCUSSION

The present study provides the first systematic characterization of ultrasonographic findings suggestive of DE in a large cohort of postmenopausal women undergoing routine gynecological evaluation. Hypoechoic nodules resembling endometriosis were identified in approximately 8% of women—a prevalence slightly higher than historical estimates of postmenopausal endometriosis, which have relied predominantly on isolated case reports, small surgical series, or incidental autopsy findings [9-11].

From a morphological perspective, the nodules detected in our cohort differed from the classic ultrasonographic appearance of DE detected in patients of reproductive age. Instead of solid hypoechoic nodules, often with spiculated or star-shaped contours, limited internal vascularization on Doppler, and areas of acoustic shadowing [5, 20], these postmenopausal lesions tended to exhibit a plaque-like, avascular profile, with regular and blurred margins consistent with fibrotic retraction in more than 80% of cases. Accordingly, we deem that this appearance may reflect quiescent fibrotic sequelae rather than ongoing inflammatory disease, in line with prior immunohistochemical observations [21], occasionally brought to light only because of a dedicated endometriosis-oriented ultrasound examination. Moreover, in reproductive-age populations, DE most frequently affects the uterosacral ligaments (52.7–69.2%), rectovaginal septum and vagina (12.0–16.2%), bowel (9.9–22.7%; rectosigmoid/rectum), and bladder (6.3–6.4%) [22, 23]; this anatomical distribution is confirmed also in the current study, given that the totality of nodules were found in the posterior pelvic comportment.

Our multivariable analysis (**Table 3**) offers additional insights. First, we observed a strong association between posterior hypoechoic nodules and time elapsed since menopause. The prevalence of nodular findings was highest within the first five years after menopause and declined sharply thereafter, with no further substantial decrease beyond this early postmenopausal window (approximately 14% vs 4–5%). In line with this descriptive pattern, women within five years of menopause had an approximately threefold higher adjusted odds of nodular findings than those more than ten years

beyond menopause. This non-linear trend suggests that detectability of residual lesions is time-dependent rather than age-dependent in a persistently hypoestrogenic environment [24], potentially reflecting progressive tissue remodeling and/or reduced sonographic conspicuity over time. Accordingly, chronological age did not add explanatory value once time since menopause was considered, supporting the latter as a more biologically meaningful metric in this context.

The dissociation between historical and current symptomatology represents another salient aspect of the current findings. A history of dysmenorrhea and chronic pelvic pain during reproductive life emerged as a consistent independent predictor of postmenopausal nodular findings (approximately a twofold higher adjusted odds), whereas current pelvic, sexual, or bowel symptoms showed no association. This observation reinforces the concept that postmenopausal nodules may largely represent quiescent fibrotic remnants of previously active disease rather than lesions driving ongoing symptom generation. Nevertheless, in postmenopausal women, pelvic and genital symptoms are frequently influenced by age-related and hypoestrogenic changes—including vaginal atrophy, urinary dysfunction, and pelvic floor disorders—which may obscure or outweigh any symptom contribution from residual endometriotic lesions [25, 26]. Importantly, this interpretation remains inferential: histological confirmation was not routinely obtained because it was not clinically indicated in most cases, and our work therefore provides an initial descriptive characterization of these postmenopausal imaging findings.

The lack of an independent association between nodular findings and HRT in our cohort warrants careful interpretation. Symptom exacerbation or lesion growth has been described in postmenopausal women receiving HRT—particularly unopposed estrogen—although absolute risks of recurrence and malignant transformation are difficult to quantify, and the impact of HRT on these outcomes remains uncertain [26]. Although systemic HRT exposure was not associated with an increased likelihood of posterior nodules in our analysis, the limited number of exposed women and the cross-sectional design preclude definitive conclusions regarding subtle effects on lesion persistence or growth. Moreover, the primary endpoint of this study was structural rather than a dynamic assessment of

hormonally driven activity. As such, our findings should not be interpreted as evidence of hormonal neutrality, but rather as an absence of detectable structural differences within the limits of the available data.

A single case in our cohort underscores the risk of misclassification in postmenopausal women, particularly when hypoechoic nodules are detected in "red-flag" sites such as the rectum or bladder, where malignancies may mimic endometriotic morphology [27, 28]. In our series, a rectal nodule detected at TVS was ultimately diagnosed as rectal adenocarcinoma (with no evidence of endometriosis), highlighting the need for caution when interpreting posterior compartment lesions in this age group. Although TVS is not a first-line tool for colorectal cancer, it may incidentally identify rectal or rectosigmoid masses during pelvic assessment and, in selected cases, prompt further diagnostic work-up [29]. Crucially, alarm symptoms—including rectal bleeding, iron-deficiency anemia, or new-onset bowel habit changes—mandate dedicated colorectal evaluation and should not be attributed to presumed endometriosis. In this context, ultrasound should be framed as an opportunistic trigger rather than a substitute for organized screening pathways (FOBT/FIT and colonoscopy). A similar caveat can be raised theoretically for the urinary bladder: focal bladder wall thickening may mimic anterior compartment endometriosis on ultrasound yet represent urothelial malignancy, particularly when accompanied by macroscopic hematuria [30]. Given the relative rarity of bladder involvement in this setting, we did not observe this scenario in our cohort; however, its potential clinical implications in postmenopausal women support heightened vigilance and a low threshold for urological assessment when suspicious imaging features or relevant symptoms are present.

Adnexal findings in our cohort provide a complementary perspective. Three of the four women had endometrioma-like cystic formations with atypical ultrasonographic features, a finding consistent with age-related changes described in the literature, as endometriomas in older women more frequently display non-classical patterns [13]. In our series, one surgically treated adnexal lesion was diagnosed as a FIGO stage I ovarian tumor (**Figure 4a**), underscoring the clinical relevance of

identifying persistent cysts with atypical “endometrioma-like” morphology in postmenopausal women. Given that endometriosis is a recognized precursor background for endometrioid and clear-cell ovarian carcinoma, persistent or atypical adnexal lesions after menopause warrant careful evaluation [31]. Serum tumor markers (CA125, HE4) and multiparametric risk models (e.g., IOTA ADNEX) may support risk stratification, although their performance has not been validated explicitly in asymptomatic postmenopausal women with newly detected small lesions resembling endometriomas with atypical morphology. Accordingly, meticulous morphological assessment, contextual interpretation of biomarkers, and short-interval follow-up or surgical management remain essential [32, 33].

This study has several strengths, including its prospective design, relatively large sample size, and the use of a standardized, endometriosis-oriented TVS protocol applied by an expert operator with systematic recording of morphology and soft markers, supported by detailed clinical phenotyping and multivariable analysis. However, some limitations must be acknowledged. Women with a previous surgical or radiological diagnosis of endometriosis were excluded, which reduces ascertainment bias and enables a focused evaluation of incidentally detected, previously unrecognized postmenopausal lesions, but limits generalizability and may underestimate the overall prevalence of postmenopausal endometriosis sequelae. Histologic confirmation was not obtained because surgery was rarely clinically indicated; therefore, lesion characterization remains presumptive and based on imaging. The single-operator and cross-sectional design precludes assessment of inter-observer reproducibility, lesion evolution over time, and causal inferences regarding symptoms or hormonal exposure. Finally, the population consisted of women attending a regional outpatient clinic for routine gynecological visits, which may introduce selection bias and limit extrapolation to the general postmenopausal population.

CONCLUSIONS

This study provides the first systematic ultrasound characterization of lesions suggestive of DE and endometriotic cysts in postmenopausal women. Such findings were relatively frequent and displayed a predominantly thin, plaque-like, avascular morphology consistent with quiescent fibrotic sequelae of previously unrecognized reproductive-age disease. Their presence was not associated with current symptoms, underscoring their limited clinical impact in most women. However, atypical features or alarm symptoms require careful evaluation to exclude malignancy. Overall, these results refine the understanding of endometriosis beyond menopause and highlight the value of expert imaging in differentiating benign fibrotic residues from clinically relevant pathology.

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