

There are 3 types of endometriosis lesions—endometriomas, which affect the ovary; superficial lesions; and deep infiltrating endometriosis. Peritoneal lesions may vary widely in appearance. Some may be clear or red; others brown, blue, or black; and some may have a white, scar-like appearance. To identify this elusive disease, it is critical that the clinician be able to recognize its “many faces.”

FIRST OF A 3-PART SERIES

Endometriosis: Expert answers to 7 crucial questions on diagnosis

📌 The notorious delay in diagnosis associated with this condition stems in part from its ability to mimic other diseases. The expert answers provided here are designed to help guide your assessment of the patient and achieve a timelier diagnosis.

Janelle Yates, Senior Editor

CASE Is her chronic pelvic pain caused by endometriosis?

M.L. is a 32-year-old nulliparous woman who is referred to your office by her primary care provider for chronic pelvic pain. She reports severe dysmenorrhea as her main symptom, but she also mentions dyspareunia. She says these symptoms have been present for several years but have increased in intensity gradually. She asks what you consider to be the most likely diagnosis.

What potential diagnoses do you mention to her? And how do you identify the cause of her pain?

Although endometriosis—the presence of endometrial tissue outside the uterus—affects at least 5 million women of reproductive age in the United States alone, it can be a challenging diagnosis for several reasons.

“Endometriosis is a great masquerader,” says Linda Giudice, MD, PhD. “It presents with a variety of pain patterns, intensities, and triggers. It can also involve symptoms that overlap those of other disorders, including disorders of the gastrointestinal and urinary tracts.”

Although endometriosis falls within the differential diagnosis of chronic pelvic pain, “it is usually not high on the list in the primary care setting (adult and adolescent),”

Dr. Giudice adds. She is the Robert B. Jaffe, MD, Endowed Professor in the reproductive sciences and chair of obstetrics, gynecology, and reproductive sciences at the University of California, San Francisco.

John R. Lue, MD, MPH, an author of the most recent practice bulletin on endometriosis from the American College of Obstetricians and Gynecologists,¹ sees the situation similarly.

“The main challenge in the diagnosis of endometriosis is that its presentation mimics other causes of chronic pelvic pain,” he says. **“Pelvic pain due to endometriosis is usually chronic (lasting ≥6 months). It is associated with dysmenorrhea in 50% to 90% of cases, as well as with dyspareunia, deep pelvic pain, and lower abdominal pain with or without back and loin pain.** The pain can occur unpredictably and intermittently throughout the menstrual cycle or it can be continuous. In addition, it can be dull, throbbing, or sharp and may be exacerbated by physical activity.^{2,3} Up to 20% of women with endometriosis have concurrent pain conditions.”⁴ Dr. Lue is associate professor, chief of the section of general obstetrics and gynecology, and medical director of women’s ambulatory services at the Medical College of Georgia and Georgia Regents University in Augusta, Georgia.

Among **other diseases of the female**

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pelvis that have relatively similar presentation, Dr. Lue adds, are pathologies of the:

- uterus (adenomyosis, fibroids)
- fallopian tube (hydrosalpinx)
- ovaries (ovarian cysts)
- bladder (interstitial cystitis)
- bowel (irritable bowel syndrome)
- musculoskeletal system (piriformis syndrome).

Before pelvic pain is attributed to endometriosis, he says, the provider should rule out bowel, bladder, musculoskeletal, and psychiatric causes.

This article focuses on 7 questions, the answers of which are critical to narrowing in on the diagnosis of endometriosis, including essential factors to consider in the patient history, imaging and other diagnostic tools, and considerations in surgical exploration. In the second and third installments of this

in-depth series on endometriosis, pain and infertility will be the respective subjects of investigation.

1. Why such a long delay in diagnosis?

Investigators exploring the length of time between a patient's presentation with symptoms and diagnosis have found it to be particularly long for endometriosis, ranging from 6 to 11 years.

Because endometriosis is usually not high on the list of differential diagnoses for chronic pelvic pain in the primary care setting, a patient may not be referred to a gynecologist unless those symptoms include severe dysmenorrhea, dyspareunia, or similar findings. Once the referral is made, **the gynecologist "will usually try contraceptive steroids, nonsteroidal anti-inflammatory drugs, or second-line progestins before a diagnosis is made," says Dr. Giudice.**⁵

The delay in diagnosis "is astounding," she adds, "and has its roots in empiric medical therapies and a combination of patients fearing a diagnosis of cancer and reluctance of gynecologists to perform laparoscopy on adolescents."⁶

Another possible cause of diagnostic delay: Some adolescent girls may not realize when their pain is severe. Because they may have always experienced a high degree of pain since menarche, they may assume it to be a normal aspect of womanhood and delay seeking help, says Pamela Stratton, MD, chief of the gynecology consult service at the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

2. Have any biomarkers proved to be useful diagnostic tools?

Any biomarker proven to reliably identify endometriosis would be a boon to medicine, as it would provide a noninvasive or minimally invasive alternative to diagnostic laparoscopy, the current gold standard. Regrettably, the search for such a biomarker has produced "disappointing results," says Dr. Giudice.

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Several theories explain the “why” of endometriosis

A dominant theory is that peritoneal endometrial implants arise from retrograde menstruation, during which endometrial tissue passes through the fallopian tubes into the pelvis, says John R. Lue, MD, MPH. Dr. Lue is associate professor and chief of the section of general obstetrics and gynecology and medical director of women’s ambulatory services at the Medical College of Georgia and Georgia Regents University in Augusta, Georgia.

“Additional theories include immune dysfunction that interferes with clearing of endometrial lesions in the pelvis, as well as genetic alterations that lead to growth dysregulation,” he says.¹ “These theories all have merit, and it is likely that the pathogenesis of endometriosis is multifactorial.”

Another strong theory involves the homeobox (HOX) genes, “which mediate embryonic development,” says Dr. Lue.^{2,3} “These genes are translated into transcription factors that regulate downstream genes necessary for growth and differentiation. It has been demonstrated that HOX genes play an analogous role in endometrial development during the adult menstrual cycle.⁴ HOX gene expression regulates the growth and development of the human endometrium.⁵ The expression of HOX genes A10 and A11 varies in response to sex steroids during the menstrual cycle, with dramatic upregulation in the mid-secretory phase,” says Dr. Lue. Recent studies suggest that these genes “play a major role” in endometriosis.⁶

“Since ovarian endometriomas are clonal and lesions usually have genetic mutations, such somatic mutations with subsequent growth dysregulation may also be etiologic factors,” says Dr. Lue.^{1,7,8} “Disease at distant sites may be caused by lymphatic or hematogenous spread or metaplastic transformation.”

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“Recent systematic reviews of all proposed endometriosis-related biomarkers over the last 25 years in serum, plasma, urine, and endometrium could not identify an unequivocally clinically useful biomarker or panel of biomarkers,” she notes.^{7,8} “This is due mainly to low numbers of subjects, small populations for validations, cycle/hormonal- and disease stage-dependence,

poorly defined controls, and low sensitivity and specificity.”

One hopeful development: “Whole genome transcriptomics of archived endometrial tissue and machine learning found several classifiers to diagnose and stage endometriosis with high accuracy that were validated on an independent sample set,” says Dr. Giudice.⁹ “However, these data now warrant a prospective, multisite study for further validation.”

3. What aspects of the patient history are key?

Dr. Stratton recommends that clinicians begin their evaluation of the patient with pain by asking her to describe that pain—how long she has had it, when it occurs, and which areas are affected.

“Most women with endometriosis-associated pain have chronic pelvic pain,” Dr. Stratton continues.⁵ “Up to 90% of those have dysmenorrhea or cyclic pain with menses.”¹⁰ In addition, women with endometriosis “commonly report having pain with any bleeding or spotting. About 30% of women diagnosed with endometriosis initially present to their gynecologist with dyspareunia.”¹¹

“Episodic pain with menses may become more constant, lasting for many days of the month,” says Dr. Stratton. “Women with dyschezia or dysuria may have endometriosis lesions associated with the bowel or bladder, respectively.¹² When women with these symptoms do not have lesions on bowel or bladder, these pain symptoms may occur because of higher peritoneal hormone and inflammatory factor levels or because adjacent organs share the neural networks.”

Dr. Giudice views the history similarly.

“I believe listening to the patient is essential in evaluating the possibility of her having endometriosis. This involves asking her to describe where her pain is, grading it on a scale of 1 to 10, identifying when in her cycle it occurs, and learning what makes it better or worse,” she says.

“It also is important to assess the quality of the pain,” Dr. Giudice says. “Does it radiate,

does it limit her daily activities, does it interfere with her relationships, intercourse, work, school? Is it associated with bowel movements, urination, other pain syndromes?”

“Having a pain questionnaire is a great help so that patients have a chance to reflect on these and other questions that help to frame the pain associated with endometriosis when they come for consultation,” she adds.

By determining if pain is associated with menstruation or spotting, the clinician is better informed about the value of menstrual suppression, says Dr. Stratton. “Determining what makes the pain better or worse can help define triggers which, if treated, can decrease the likelihood of episodes of pain.”

“A detailed history of any medical or surgical treatments and their outcome is helpful in guiding future treatment,” she adds. “While hormonal therapy has been a mainstay of treatment, in some women, some hormonal treatments may worsen pain or have unacceptable side effects like worsening depression or anxiety. In addition, some pain—especially that associated with deep lesions—may be relieved by surgical treatment^{13,14}; pain that worsened after surgery may suggest neural damage.”

“As there is an engagement of the central nervous system, endometriosis is considered a central sensitivity syndrome in which women may also have other sites of pain,” Dr. Stratton says. “Thus, obtaining a history about current symptoms or prior diagnosis of irritable bowel syndrome, interstitial cystitis/painful bladder, migraines, fibromyalgia, or chronic fatigue syndrome is beneficial.^{10,15-17} Facilitating treatment for these comorbidities is a key principle in helping women with endometriosis-associated pain, as **any condition that triggers or perpetuates pain warrants treatment.**”

4. What should the physical exam entail?

“An abdominal exam and a pelvic exam are essential in evaluating pain in a woman when endometriosis is suspected,” says Dr. Giudice. “Sometimes the latter is

challenging in young teens and can be deferred.” Overall, however, “the pelvic exam can give insight into pain triggers, adnexal masses (possible endometriomas) and mobility of pelvic organs. A rectovaginal exam is important in evaluating deep infiltrating disease and to gauge the pelvic pain landscape overall. In addition, palpating the pelvic floor musculature is important to distinguish pelvic floor muscle spasm from endometriosis pain.”

“The challenge for clinicians is to think beyond the endometrial implants, taking into account multiple factors that influence pain perception,” says Dr. Stratton. During the examination, the clinician should begin by mapping the regions of pain in the abdomen and back, “distinguishing musculoskeletal pain from deep pain. Determining whether pains are focused or diffuse is also important.”

Dr. Stratton recommends that the routine pelvic exam be modified because a standard bimanual exam “confuses pain signals from the pelvic floor, abdominal wall, bladder, and other viscera. For this reason, a pain-oriented assessment is mandatory.”

Begin with a single digital examination to map tender areas, Dr. Stratton advises. Then consider the size, shape, and mobility of reproductive and pelvic organs. “A bimanual exam will help identify adnexal masses like endometriomas,” she says.

Endometriomas usually are not associated with pain, she adds, but “they are associated with deep infiltrating lesions. Nodularity along the uterosacral ligaments, limited reproductive organ mobility, and thickening of the rectovaginal septum also suggest deep infiltrating lesions. Importantly, deep infiltrating lesions are the lesion type most associated with pain.”^{18,19}

5. Is imaging useful in the diagnosis of endometriosis?

Laparoscopy remains the gold standard for diagnosis of endometriosis, observes Steven R. Goldstein, MD. Visualization of endometriotic implants at the time of surgery—with histologic assessment—



Although hormonal therapy has been a mainstay of endometriosis treatment, it may worsen pain in some women

offers definitive confirmation of the diagnosis. The physical examination, too, can offer a strong suggestion of endometriosis, he says. Dr. Goldstein is professor of obstetrics and gynecology at New York University School of Medicine and director of gynecologic ultrasound and co-director of bone densitometry at New York University Medical Center in New York City. He serves on the OBG MANAGEMENT Board of Editors.

“In the past, the pelvic examination and history often were the sine qua non for patients with pain,” Dr. Goldstein says. “Extreme dysmenorrhea and pain between periods, especially with intercourse, defecation, and exercise, all increased the suspicion of endometriosis. People used to talk about feeling nodularity in the uterosacral ligaments and finding decreased mobility of pelvic structures—but I don’t have any question that the skill of today’s gynecologists in doing a bimanual pelvic exam is a fraction of what it was in years gone by because they haven’t had the necessity of experience. The first thing they do if there’s any question is they send the patient for an ultrasound.”

Of course, ultrasound can be especially helpful in identifying endometriomas—sometimes called “chocolate cysts”—in the ovary. Endometriomas can have a solid appearance on ultrasound, says Dr. Goldstein, because the fluid they contain (dried blood) is sonolucent or pure black on ultrasound, similar to amniotic fluid or the fluid seen in the bladder. “This ‘chocolate’ fluid contained in endometriomas is homogeneous, particulate, and very monotonous in its appearance, in contrast to the internal echoes observed in hemorrhagic corpus lutea, which are very cobweblike and can sometimes mimic papillary projections,” he adds.

“What’s absolutely essential when imaging a suspected endometrioma by ultrasound is that there be no evidence of any blood flow contained within that structure. Because it’s dried blood, it shouldn’t have any vascularity. **If you see blood flow inside what you would call an endometrioma, you need to rethink your diagnosis,**” he says.

In some cases, a supposed endometrioma

lacks a black, sonolucent appearance, but “the clinician often can tell that it’s a cystic structure by the very bright posterior wall—what we call posterior wall acoustic enhancement—even though the interior of the structure may appear sort of grayish or whitish rather than the pure black of a simple cyst. It’s still fluid-filled,” Dr. Goldstein says.

In some instances, even endometriotic nodules can be imaged by ultrasound, he adds. “There’s an increasing body of literature that suggests that, if you look carefully in people with deep infiltrating endometriosis, you can often see solid-appearing nodules in the rectovaginal septum or between the uterus and bladder. With the kind of resolution that we now have with the vaginal probe, some of these nodules can be seen. That’s somewhat new, and it’s a function of 2 things—people looking for endometriosis and the better resolution of more modern equipment.”

Dr. Goldstein believes that magnetic resonance imaging (MRI) is “almost never” indicated in the diagnosis of endometriosis. A more helpful approach would be a consultative ultrasound with someone with more experience. However, when that is not available, or “in areas where you have excellent backup in terms of pelvic MRI, that may be the way to go. I don’t think so,” he demurs, “and some of my colleagues would be very upset at the thought of needing to use MRI to diagnose endometriosis. But in the occasional confusing or difficult case, depending on the quality of the referral pattern you have, it might make sense,” he says.

6. When is diagnostic laparoscopy clearly indicated?

Dr. Giudice believes that laparoscopy—with the intention to treat endometriosis, if present—“is essential when first-line medical therapy fails or when pain is acute and severe.”⁵

Dr. Stratton concurs. “Any woman with chronic pain wants to know what is causing the pain,” she says. Therefore, “women report a benefit from knowing that their pain is associated with endometriosis.”⁶ However, **diagnostic laparoscopy alone, with the sole**



MRI is almost never indicated in the diagnosis of endometriosis

purpose of determining the presence of endometriosis but not treating the lesions, is no longer performed, as it poses little benefit to the patient other than peace of mind.”

“The general trend in the United States has been to first use hormonal treatments when the diagnosis of endometriosis is suspected, prior to performing surgery,” Dr. Stratton says.¹ In many cases, by using cyclic combined hormonal contraceptives to reduce menstrual flow or “suppressing menstruation with continuous combined hormonal contraceptives,” gonadotropin-releasing hormone analogues (combined with progestin to prevent bone loss), “or continuous progestin alone may be effective in decreasing pain. Not surprisingly, these hormonal approaches are effective for any chronic pelvic pain, even for women who do not have the surgical diagnosis of endometriosis.”²⁰

“When the first-line approach to chronic pelvic pain is hormonal treatment, laparoscopy is considered when these medical treatments have failed to control the pain or are poorly tolerated, or when the diagnosis of endometriosis is in question,” Dr. Stratton says.

“Laparoscopy to treat endometriomas is indicated if an endometrioma is enlarging, measures more than 4 cm in diameter, or if the diagnosis of an ovarian mass is in question,” she explains. “While surgeons have previously been aggressive in removing endometriomas, this practice may have negative consequences on ovarian function. Because endometriomas are pseudocysts, removing them completely leads to the removal of viable ovarian tissue and may diminish ovarian reserve.”^{21,22}

7. What is the surgical appearance of endometriosis?

Dr. Giudice returns to the enigmatic nature of endometriosis in addressing this question, mentioning its “many faces” at the time of surgery. “It is imperative that the surgeon recognize the disease in its many forms,” she says. “Also, it is especially helpful at the time of surgery if suspected lesions are biopsied

Environmental factors, estrogen, and endometriosis

“There is increasing evidence that in utero and also adult exposures to endocrine-disrupting chemicals (EDCs) play a role in the pathogenesis and progression of disease,” says Linda Giudice, MD, PhD, the Robert B. Jaffe, MD, Endowed Professor in the reproductive sciences and chair of obstetrics, gynecology, and reproductive sciences at the University of California, San Francisco.

“For example, the Nurses’ Health Study II, a prospective cohort study of more than 80,000 women, revealed that daughters exposed to diethylstilbestrol (DES) had an 80% increased risk (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.2–2.8) of developing endometriosis,” she says.¹

“Also, dioxin (TCDD) exposure in rats in utero on gestational day 8 increased the size of endometriosis lesions when combined with an adult exposure,” Dr. Giudice says.² Although we do not know the precise mechanisms underlying in utero events that result in disease onset as a teen or adult, abnormal programming of the female reproductive tract by EDCs and similar agents is believed to play a role, she says.³

Because estrogen is essential for endometriosis lesions and associated symptoms to progress, “EDCs that have either estrogenic activity or interfere with estrogen metabolism or action, or both, have been proposed as contributors to progression of disease. Abundant animal data using nonhuman primate and rodent models and exposures to organochlorines and other EDCs support this hypothesis,” Dr. Giudice says.⁴

“The weight of human evidence of associations of EDCs and the risk of endometriosis in adult women depends on the class of endocrine disrupter,” Dr. Giudice continues. “Strongest correlations are with polychlorobiphenyls (PCBs), where 10 of 12 studies found significant odds of disease and circulating or omental fat concentrations of these compounds. PCBs inhibit peripheral natural killer cell activity and interleukin 1b and 12 production, relevant to the immune component of endometriosis progression.”

“Significant risk has also been associated with organochlorines (in three of three studies) and perfluorochemicals. In contrast, data linking endometriosis with exposures to dioxins, phthalates, and bisphenol A are equivocal, with some studies finding significant odds ratios and others failing to find significant correlations. Interestingly, dioxins have a significant association with deep infiltrating endometriotic lesions.”⁵

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and sent to pathology to have the diagnosis made unequivocally.”⁵

As for the surgical appearance of endometriosis, Dr. Stratton notes that there are 3 types of lesions—“superficial lesions, deep infiltrating lesions, and endometriomas. Endometriomas occur almost exclusively in the ovary and are pseudocysts without an identifiable cystic lining. They vary in dimension from a few millimeters to several centimeters.”


“Superficial peritoneal endometriosis lesions have a variable appearance, with some lesions being clear or red, some brown, blue or black, and some having a white appearance, like a scar,” says Dr. Stratton. “Endometriosis can be diagnosed on histologic examination of any of these lesion types.

“Overall, single-color lesions have similar frequencies of biopsy-confirmed endometriosis (59% to 62%),” she says.²³ “These lesion appearances likely represent different stages of development of endometriosis, with red or clear lesions occurring first, soon after endometrial tissue implantation; black, blue, or brown lesions occurring later, in response to the hormones varying in the menstrual cycle; and white lesions occurring as the lesions age. Deep infiltrating lesions generally have blue/black or white features.”

“Wide, deep, multiple-color lesions in the cul-de-sac, ovarian fossa or uterosacral ligaments are most likely endometriosis,” Dr. Stratton adds.²³ Only lesions with multiple colors have a significantly higher percentage of positive biopsies (76%). Importantly, over half of women with only subtle lesions (small red or white lesions) have endometriosis.

CASE Resolved

You tell the patient that endometriosis is one of the possible diagnoses for her chronic pelvic pain, and you take a focused history. During a pelvic examination, you observe that her right ovary lacks mobility, and you map a number of trigger points for her pain. Transvaginal ultrasound results suggest the presence of nodules in the rectovaginal septum. You begin empiric treatment with continuous combined hormonal contraceptives to suppress menstruation. On her next visit, the patient reports reduced but

still bothersome pain. Laparoscopy reveals a 2-cm endometrioma in the right ovary and deep infiltrating lesions in the cul-de-sac. The endometrioma is resected. Histology confirms the diagnosis of endometriosis. 

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