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Invasive and non-invasive methods for the diagnosis of endometriosis

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Abstract

Endometriosis has been associated with pain and infertility. The gold standard for the diagnosis of endometriosis has been visual inspection by laparoscopy, preferably with histological confirmation. Because there is no good noninvasive test for endometriosis, there is often a significant delay in diagnosis of this disease. Imaging that confirms an endometriotic cyst or deep infiltrating endometriosis may help guide surgical therapeutic approaches. No serum marker has been found to diagnose endometriosis with adequate sensitivity and specificity. There has been a recent focus on the presence of nerve fibers in the eutopic endometrium of patients with endometriosis.

Keywords

endometriosis; diagnosis; laparoscopy; ultrasound; magnetic resonance imaging; endometrioma; deep infiltrating endometriosis

Endometriosis is a common benign gynecologic disorder, defined by endometrial glands and stroma outside of the endometrial cavity. Endometriosis can be associated with infertility or pain symptoms, including cyclic pelvic pain, dysmenorrhea, dyspareunia, dysuria, and dyschezia. The correlation between lesions and pain symptoms or infertility in endometriosis is poorly understood. There is a wide spectrum of symptom severity, and the stage of endometriosis on laparoscopy correlates poorly with the extent and severity of pain. Some patients with minimal disease have debilitating pain, while other women with severe stage III–IV disease are asymptomatic.

Up to 20% of women with endometriosis have concurrent chronic pain conditions, including irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, fibromyalgia, and migraines.[1] Prior to attributing pelvic pain to endometriosis, bowel, bladder, psychiatric, and musculoskeletal etiologies should be ruled out. Given that endometriosis may be a diagnosis of exclusion, the diagnosis of endometriosis in a woman with pelvic pain is often delayed and stretches over several years.[2]

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Diagnosis of endometriosis may affect the management of pain or infertility, and thus should be considered in patients with these symptoms. For patients with pain in whom endometriosis is suspected, empirical Non-steroidal anti-inflammatory drugs (NSAIDs) or hormonal treatment (such as continuous oral contraceptive pills) is usually the first option. Patients with pain refractory to these treatments may benefit from diagnostic and operative laparoscopy, ideally with biopsy of at least one lesion to confirm the diagnosis. There are many options for the management of infertility (without pain) associated with minimal or mild endometriosis; these range from laparoscopic diagnosis and laparoscopic treatment to direct referral to an infertility center. The optimal fertility strategy in women with endometriomas is unknown. Discussion of the relative merits of treatment options for infertile women with suspected endometriosis is outside the scope of this article.

This article will focus on the invasive and noninvasive diagnosis of endometriosis, in the context of pain symptoms or infertility. The diagnostic value of laparoscopy, imaging, serum markers, or endometrial biopsy depends on clinical context and treatment goals. For example, diagnosing endometriosis in an asymptomatic patient with proven fertility is of limited utility. The ideal noninvasive diagnostic marker for endometriosis should both predict the presence of symptomatic endometriosis and help monitor treatment.

Types and locations of endometriotic lesions

The three primary types of endometriosis are superficial peritoneal lesions, ovarian endometriomas, and deep infiltrating endometriosis (DIE). While all three types of lesions are associated with chronic pelvic pain, the location and extent of lesions correlate poorly with the location and severity of experienced pain. However, some lesion characteristics described at the end of operative laparoscopy may be predictive of subsequent fertility.[2]

Superficial lesions of endometriosis are typically located on the pelvic organs or pelvic peritoneum. The classic bluish or blue-black “powder-burn” lesion resembles the endometrium and may be associated with hemosiderin deposits. Non-classic lesions include clear and red “flame-like” lesions or white lesions. The metabolic activity and symptoms associated with lesion types are hypothesized to vary, but this has not been well studied. Endometriosis can also be found in the base of a peritoneal defect called an “Allen-Masters” window.

Endometriomas contain a dense, brown, chocolate-like fluid and are pseudocysts formed by the invagination of endometriosis within the ovarian cortex. Adhesions are usually associated with endometriomas and attach them to nearby pelvic structures. Deep infiltrating endometriosis (DIE) is a nodular blend of fibromuscular tissue and adenomyosis.[4] These lesions are primarily found in the uterosacral ligaments or cul de sac, but may also involve the rectovaginal septum. Patients with DIE may present with deep dyspareunia and various bowel symptoms from diarrhea to dyschezia during menses, depending on the location of the deep lesions.

Endometriosis is primarily found in the pelvis: on the ovaries, uterus, fallopian tubes, uterosacral ligaments, broad ligaments, round ligaments, cul-de-sac or ovarian fossa, as well as on the appendix, large bowel, ureters, bladder, or rectovaginal septum. Extra-pelvic locations of endometriosis are rare, but can include the upper abdomen, diaphragm, abdominal wall or abdominal scar tissue. Diagnosis of endometriosis at these various sites has been made using magnetic resonance imaging (MRI), cystoscopy (for bladder endometriosis), sigmoidoscopy or colonoscopy (for transmural bowel lesions) and ultrasound-guided fine needle aspiration (FNA: for endometriosis in the rectosigmoid, rectovaginal septum, or in abdominal scars). Unusual sites of endometriosis can present with atypical symptoms, including cyclic hematochezia, hematuria or even hemoptysis.

Clinical diagnosis

A complete history and physical examination, including speculum and bimanual examination, may aid in diagnosis. As an estrogen-dependent disease occurring in women with heavy menses, endometriosis has been suspected most commonly in women with menstrual-associated cyclic pain. Such cyclic pain is not pathognomonic for endometriosis, as women with fibroids and adenomyosis may also have dysmenorrhea. Furthermore, many patients with endometriosis have non-menstrual chronic pelvic pain, complaining of pain at other predictable times of their menstrual cycle, such as at ovulation. Patients may also have dyspareunia, bowel or bladder pain, or chronic fatigue.

Patients with endometriosis may also suffer from other pain syndromes such as painful bladder syndrome, irritable bowel syndrome, fibromyalgia, and migraines. Endometriosis may be associated with bowel or bladder symptoms which include constipation, diarrhea, or hematochezia or cyclic urinary frequency or urgency. Such symptoms may help guide clinical investigations and imaging. Gastrointestinal symptoms and dyschezia have been associated with DIE lesions in the bowel, dyspareunia is increased with DIE lesions in the uterosacral ligaments, and severe dysmenorrhea has been associated with cul-de-sac adhesions.[5] However, gastrointestinal and genitourinary diseases should always be considered before attributing symptoms to endometriosis.

Often, no abnormalities are found on the physical examination of patients with endometriosis, and speculum exam is rarely helpful for making the diagnosis. However, focal tenderness or nodularity of the uterosacral ligaments or the cul-de-sac may be apparent on bimanual exam. An enlarged, tender, cystic adnexal mass may suggest an endometrioma. A fixed retroverted uterus or a “frozen pelvis” can be assessed on exam or by MRI, which may suggest the need for bowel preparation prior to surgery. While some have proposed that uterosacral nodularity is better palpated during menses, no studies have conclusively demonstrated this observation. In fact, the poor negative predictive value of the pelvic exam was demonstrated in one study of 91 patients, in which 47% of patients with surgically confirmed endometriosis and chronic pelvic pain had normal bimanual examinations.[6] Although the physical examination has poor sensitivity, specificity, or predictive value in the diagnosis of endometriosis, findings on examination can suggest the benefit of imaging prior to surgery.

Some patients present with severe pain and have difficulty tolerating non-painful stimuli, including a speculum or bimanual exam; such a response to typically non-painful stimuli is called hyperalgesia. These patients often also have allodynia (exaggerated response to pain stimuli) and reduced pain tolerance. When such severe, systemic pain occurs in women with endometriosis, it may not respond to operative laparoscopy or to hormonal treatment. While it may be useful to diagnose endometriosis in these patients, they may suffer from multiple concurrent pain syndromes. In such cases, these patients may benefit from a multi-faceted approach to chronic pain, involving an interdisciplinary team that includes pain specialists, urologists, gastroenterologists, and other non-gynecologists.[1]

Laparoscopy

At laparoscopy, endometriosis may be visualized as peritoneal implants, peritoneal windows, endometriomas, and deep infiltrating nodules of endometriosis which may each be associated with adhesions. The color, size, and morphology of endometriotic lesions are highly variable from person to person. Endometriotic implants in the pelvis occur more often on the left side, although the reason for this asymmetry is not known. On histopathology, the diagnosis of endometriosis requires the presence of two or more of these histologic features: endometrial epithelium, endometrial glands, endometrial stroma, and hemosiderin-laden macrophages.[7]

In several studies, visual diagnosis of endometriosis has been demonstrated to be unreliable. Only 54–67% of suspected endometriotic lesions are confirmed histologically, and 18% of patients clinically suspected to have endometriosis have no evidence of endometriosis on pathology.[8] Indeed, a 2004 metaanalysis which assumed a 20% prevalence of endometriosis found that "a positive finding on laparoscopy will be incorrect in half of the cases."[9]

In these circumstances, peritoneal lesions may actually be inflammatory changes, hemangiomas, foreign body reaction, mesothelial hyperplasia, and hemosiderin deposits rather than endometriosis. Interestingly, biopsy of normal-appearing peritoneum has revealed endometriosis in 6% of women with no visible lesions,[10] and up to 25% of asymptomatic infertile women. In summary, laparoscopic visualization of peritoneal lesions alone is of limited accuracy, and if a diagnostic laparoscopy is performed, confirmatory biopsies of peritoneal lesions, even atypical ones, will be of value. The lesions most likely to be histologically confirmed as endometriosis are generally large, mixed-color lesions in the cul de sac or on the uterosacral ligaments.[11]

Laparoscopy is useful for the diagnosis of endometriomas, as they are easily visualized and are often associated with ovarian adhesions. Inspection and biopsy of the cyst wall surface is important to exclude ovarian neoplasm. Stripping the endometriotic cyst wall from the ovary is advised because of the high recurrence rate after laparoscopic drainage of an endometrioma without removal. However, operative treatment of endometriomas is also associated with diminished ovarian reserve and premature ovarian insufficiency. Thus, operative treatment of endometriomas is controversial in women desiring future fertility.

The extent of deep infiltrating endometriosis is difficult to gauge on diagnostic laparoscopy alone, but can be appreciated during operative laparoscopy. It is important to suspect these lesions prior to surgery, as a surgical team with appropriate expertise can be assembled and the optimal surgical approach determined. In some cases, gastrointestinal or urologic surgeons may be valuable additions to the surgical team.

Imaging

Imaging has limited utility in the diagnosis of endometriosis, as it lacks adequate resolution to identify adhesions or superficial peritoneal implants. Ultrasound is cheap and easy to perform, but user-dependent; MRI is more accurate but considerably more expensive. As CT of the pelvis does not visualize pelvic organs well, it is not useful in the diagnosis of endometriosis. An important role for the CT scan with contrast is to detect ureteral involvement and possible renal insufficiency.

Ultrasound is a readily available and inexpensive tool for the diagnosis of large endometriosis lesions. Transvaginal ultrasound can help diagnose endometriomas, bladder lesions, and deep nodules such as those in the rectovaginal septum. Lesions identifiable on ultrasound include hypoechogenic linear thickening or nodules/masses with or without regular contours. With an experienced sonographer, transvaginal ultrasound has high specificity and sensitivity in the diagnosis of ovarian endometriosis. While an adnexal mass may be suspicious for an endometrioma, the differential diagnosis includes dermoid cyst, hemorrhagic cyst, neoplasm, ovarian abscess, and ectopic pregnancy. Transrectal ultrasound may also be used to demonstrate rectal involvement in endometriosis, the depth of infiltration by endometriosis, and to detect lesions on the posterior bladder wall,[12] but it has not been shown to be superior to transvaginal ultrasound.

MRI may help guide surgical approaches for patients with suspected endometriosis, especially for deep infiltrating endometriosis and other unusual sites of presentation. Both ultrasound and MRI may suggest endometriosis, but given the significant cost differential between MRI and

ultrasound, MRI is most useful for ultrasonographically-indeterminate pelvic masses. MRI is also superior to ultrasound in diagnosing rectosigmoid lesions and endometriosis of the bladder.

Serum markers

Serum markers for endometriosis have been eagerly sought for their use in diagnosis, to measure disease activity, and to monitor improvement. Serum cytokines, matrix metalloproteinases, adhesion molecules, and markers of angiogenesis or inflammation have been investigated. While peritoneal markers have also been investigated, the cyclic variation in hormonal influences and the amount of peritoneal fluid makes this impractical and difficult to standardize. Most studies (see Table 1) have not correlated markers with disease activity or symptomatology, partly because patient populations have not been well-characterized when these markers are drawn. To date, no individual serum marker has been found to specifically correlate with the symptoms of endometriosis, and many of them are present in other conditions. As individual serum markers are nonspecific for the diagnosis of endometriosis, investigations are underway to seek whether panels of markers would be more successful.

Endometrial nerve fibers

Endometrial biopsy is being explored for the diagnosis of endometriosis. Recent studies[14,15] have shown an increased number of nerve fibers in the endometrium of women with endometriosis compared to women without endometriosis. These nerve fibers are reported to be primarily small unmyelinated sensory C fibers in the functional layer of endometrium, which are identified by their staining with PGP9.5, VIP, and substance P, but not with neurofilament. Some evidence suggests that endometriosis patients on hormonal treatment also have fewer nerve fibers compared to endometriosis patients who are not on hormones. A significant limitation in these studies is the lack of information about pain symptoms in these mixed cohorts of patients with infertility and chronic pain.

Conclusion

Studies have shown that experienced clinicians can predict the presence of endometriosis based on history and physical examination in 80% of cases. The gold standard for diagnosis of endometriosis remains laparoscopic visualization; given the protean appearance of peritoneal lesions, as well as the significant errors in diagnosis with laparoscopic visualization alone, the most suspicious peritoneal lesion(s) should be biopsied to enable histological confirmation. Preoperative imaging may be warranted based on the clinical assessment and may also help guide therapeutic approaches, enabling patient counseling prior to surgery, the possible benefit of a preoperative bowel preparation, and assembling advanced surgical specialists as needed.

A trial of empiric hormonal treatment can be useful for patients who present with pain, but is not indicated in treatment of infertility. However, those in whom hormonal therapy fails to treat symptoms may benefit from laparoscopy. The appropriate management of infertility patients with suspected endometriosis and without pain is beyond the scope of this chapter.

Transvaginal ultrasound, MRI or transrectal ultrasound can help visualize endometriomas and deeply infiltrating endometriosis. Transvaginal ultrasound is likely superior to transrectal ultrasound in the majority of cases. MRI is particularly helpful in ultrasonographically-indeterminate pelvic masses and diagnosing endometriosis of the ureters, bladder, and rectosigmoid. Imaging is inadequate for detection of pelvic adhesions or superficial peritoneal implants.

No individual serum marker has yet been shown to be both sensitive and specific for diagnosis or monitoring of endometriosis. Further research is needed to establish the potential benefit of endometrial biopsy or panels of serum markers for the noninvasive diagnosis of endometriosis. Attempts to diagnose endometriosis at unusual sites remain investigational.

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References

1. Berkley, KJ.; Stratton, P. Mechanisms: lessons from translational studies of endometriosis. In: Giamberardino, MA., editor. Visceral Pain: Clinical, Pathophysiological and Therapeutic Aspects. Oxford: Oxford University Press; 2009. p. 39-50.
2. Kennedy S, Bergqvist A, Chapron C, et al. ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod 2005;20(10):2698–2704. Updated at <http://guidelines.endometriosis.org/>. [PubMed: 15980014]
3. Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. Fertil Steril. 2009 [Epub ahead of print].
4. Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil Steril 1997;68(4):585–596. [PubMed: 9341595]
5. Fauconnier A, Chapron C. Endometriosis and pelvic pain: epidemiological evidence of the relationship and implications. Hum Reprod Update 2005;11:595–606. [PubMed: 16172113]
6. Nezhat C, Santolaya J, Nezhat FR. Comparison of transvaginal sonography and bimanual pelvic examination in patients with laparoscopically confirmed endometriosis. J Am Assoc Gynecol Laparosc 1994;1(2):127–130. [PubMed: 9050474]
7. Medical Management of Endometriosis. ACOG Practice Bulletin #11. 1999
8. Walter AJ, Hentz JG, Magtibay PM, Cornella JL, Magrina JF. Endometriosis: correlation between histologic and visual findings at laparoscopy. Am J Obstet Gynecol 2001;184(7):1407–1411. [PubMed: 11408860]
9. Wykes CB, Clark TJ, Khan KS. Accuracy of laparoscopy in the diagnosis of endometriosis: a systematic quantitative review. BJOG 2004;111(11):1204–1212. [PubMed: 15521864]
10. Balasch J, Creus M, Fabregues F. Visible and non-visible endometriosis at laparoscopy in fertile and infertile women and in patients with chronic pelvic pain: a prospective study. Hum Reprod 1997;12 (8):1794–1799. [PubMed: 9308814]
11. Stegmann BJ, Sinaii N, Liu S, et al. Using location, color, size, and depth to characterize and identify endometriosis lesions in a cohort of 133 women. Fertil Steril 2008;89(6):1632–1636. [PubMed: 17662280]
12. Bazot M, Malzy P, Cortez A. Accuracy of transvaginal sonography and rectal endoscopic sonography in the diagnosis of deep infiltrating endometriosis. Ultrasound Obstet Gynecol 2007;30(7):994–1001. [PubMed: 17992706]
13. Ballyguier C, Chapron C, Dubuisson JB, et al. Comparison of magnetic resonance imaging and transvaginal ultrasonography in diagnosing bladder endometriosis. J Am Assoc Gynecol Laparosc 2002;9(1):15–23. [PubMed: 11821601]
14. Al-Jefout M, Dezarnaulds G, Cooper M, et al. Diagnosis of endometriosis by detection of nerve fibres in an endometrial biopsy: a double blind study. Hum Reprod 2009;24(12):3019–3024. [PubMed: 19690352]
15. Bokor A, Kyama CM, Vercruysse L, et al. Density of small diameter sensory nerve fibres in endometrium: a semi-invasive diagnostic test for minimal to mild endometriosis. Hum Reprod 2009;24(12):3025–3032. [PubMed: 19690351]

16. Xavier P, Beires J, Belo L. Are we employing the most effective CA-125 and CA 19-9 cut-off values to detect endometriosis? Eur J Obstet Gynecol Reprod Biol 2005;123(2):254–255. [PubMed: 15893865]

17. Cho S, Cho H, Nam A, et al. Neutrophil-to-lymphocyte ratio as an adjunct to CA-125 for the diagnosis of endometriosis. Fertil Steril 2008;90(6):2073–2079. [PubMed: 18555226]

18. Seeber B, Sammel MD, Fan X. Panel of markers can accurately predict endometriosis in a subset of patients. Fertil Steril 2008;89(5):1073–1081. [PubMed: 17706208]

Table 1

Examples of serum markers for endometriosis

	Patients	Pain	Sensitivity (%)	Specificity(%)	PPV	NPV	Reference
CA-125	38	25	92.3	72	94.7	63.2	Xavier 2005
CA 19-9	38	25	80	53.9	76.9	58.3	Xavier 2005
CA-125	231		55,8	92,8			Cho 2008
CA-125+NLR	231		69,3	83,9			Cho 2008
CA-125+MCP-1+leptin	78	63	49	94			Seeber 2008
CA-125+MCP-1+leptin+MIF	78	63	100	40			Seeber 2008