Diagnosis of Endometriosis

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ABSTRACT

Endometriosis is a common disorder of women of reproductive age, yet diagnosis of this condition is often problematic. The most frequent clinical presentations of endometriosis include dysmenorrhea, pelvic pain, dyspareunia, infertility, and pelvic mass. However, the correlation between these symptoms and the stage of endometriosis is poor. Currently available laboratory markers are of limited value. At present, the best marker, serum CA-125, is usually elevated only in advanced stages and therefore not suitable for routine screening. Transvaginal ultrasound and magnetic resonance imaging are often helpful, particularly in detection of endometriotic cysts. Recently, transrectal ultrasound and magnetic resonance imaging were shown to be valuable in detection of deep infiltrating lesions, especially in the rectovaginal septum. Although direct assessment of endometriotic foci at laparoscopy may be viewed as a "gold standard" for identifying endometriosis, the correlation of laparoscopic observations with histological findings is often low. Ultimately, diagnosis of endometriosis requires a careful clinical evaluation in combination with judicious use and critical interpretation of laboratory tests, imaging techniques, and, in most instances, surgical staging combined with histological examination of excised lesions.

KEYWORDS: Endometriosis, laparoscopy, CA-125, imaging techniques

What is endometriosis? Upon reflection, this seemingly naive question is not easily answered. The traditional definition relies on histopathological criteria whereby ectopic endometrial stroma and glands are detected beyond the myometrium.

A narrow interpretation of this definition can easily lead to clinical paradoxes. For example, asymptomatic women with incidentally discovered microscopic foci of endometrial glandular and stromal cells would have, by definition, endometriosis. However, at present, there is no evidence supporting treatment of such a condition. Diagnosing endometriosis under such circumstances may be meaningless at best or possibly harmful when leading to unnecessary and potentially detrimental medical or surgical interventions.

In contrast, following the same strict criteria, symptomatic patients with atypical but clinically obvious disease with adhesions and multiple atypical lesions may be denied the diagnosis of endometriosis when, for example, histologic assessment of the lesions reveals only endometrial-like stroma, fibrosis, and inflammation but no obvious glands. Yet, it is apparent that such an inflexible approach to the definition of endometriosis fails to acknowledge our current understanding of the variability in lesions and their natural progression.[1]

These considerations underscore the complexity of issues surrounding the entire diagnostic process of this elusive disease. It is not surprising that the actual prevalence of endometriosis in the general population, estimated to range from 1 to 8%, is unknown.[2–4] Endometriosis is diagnosed far more frequently among women with infertility or pain, with prevalence ranging from 15 to 70%.[5,6]

This review discusses the available diagnostic tools, their advantages, and their limitations. Selectively, con-

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troversial findings are summarized. In the absence of easy and unequivocal tests, the ultimate goal of this article is to provide the clinician with a framework assisting in the process of diagnosing endometriosis. This process requires identification of patients at risk as well as a selective use of tests and their critical interpretation, preferably in the context of a complete laparoscopic and histologic assessment.

CLINICAL ASSESSMENT

Clinical presentations of endometriosis are highly diverse and none of the presenting symptoms or signs are pathognomonic for this disorder. However, a complete history and detailed physical examination assist in the identification of symptoms and signs highly suggestive of endometriosis. This is crucial because subsequently discussed diagnostic tests will have adequate positive and negative predictive value only when performed on an appropriately selected high-risk population.

History

Most risk factors for endometriosis relate to the concept of this condition being estrogen dependent and associated with reflux of menstrual effluent to the peritoneal cavity. Endometriosis is almost always detected in women of reproductive age; the mean age at diagnosis ranges from 25 to 29 years.[7,8] Endometriosis may be found in early adolescence, especially in patients with partial or complete obstructive müllerian anomalies, such as cervical atresia, or in patients with obstructed rudimentary uterine horns, whereby the disease is presumably induced by severe retrograde menstrual flow.[9–12] However, about 47 to 73% of teenagers with no outflow tract obstruction but with severe dysmenorrhea and pelvic pain not responding to analgesics are also diagnosed with endometriosis.[13–15] An association between early menarche (before age 11–13) and endometriosis was demonstrated in several, but not all, epidemiological studies.[4,16–19] Symptomatic endometriosis after menopause is rare and is usually related to hormone replacement therapy.[20,21] Nevertheless, de novo cases of endometriosis in postmenopausal women have been described.[22]

The risk of endometriosis seems to be directly related to the total amount of menstrual flow. Endometriosis is more common in women with a short menstrual cycle ($\leq$27 days), longer menstrual flow ($\geq$7 days), and spotting before onset of menses.[16,17,23]

Selected constitutional factors correlate with the risk for endometriosis. Tall women with low body mass appear to be at increased risk for endometriosis because, according to some reports, taller women tend to have shorter menstrual cycles, possibly due to reduced germ cell endowment, and/or higher chance for defective canalization of the cervix.[16,24] Endometriosis was also found more commonly in women of Asian origin than in Caucasian women.[3] Factors that may lower estrogen levels, such as smoking and regular exercise, were associated with a decreased risk for endometriosis; however, these observations were not confirmed in more recent studies.[4,16,19]

A decreased likelihood of endometriosis has also been observed in women who have been pregnant. This may be due to a protective effect of pregnancy, or it may reflect decreased fertility of patients with endometriosis. Risk of endometriosis is inversely related to the number of term pregnancies.[3,19] In a study of 817 women with infertility or pelvic pain, the odds ratio for endometriosis in multiparous women with two or more births, when compared with nulliparous women, was 0.4.[19] However, the protective effect of pregnancy appears to wane gradually and an increased risk of endometriosis has been observed with an increase in the number of years since the last childbirth.[4,25] In a case-controlled study, the odds ratio for endometriosis was 4.5 after 10 years without a birth, compared with the first 5 years after a delivery.[25]

A family history of endometriosis is relevant, especially in light of growing evidence suggesting a genetic component of the disease, probably involving a polygenic pattern of inheritance.[26–28] There is significant familial clustering, and first-degree relatives of a women with endometriosis have a sevenfold greater chance of developing the disease.[29,30] Moreover, endometriosis is more likely to develop in monozygotic than dizygotic twin sisters.[31,32] Associations between red hair, dysplastic nevi, and endometriosis have been demonstrated.[33,34] Further evidence for a hereditary component of endometriosis is provided by population genetic studies.[35–37]

From the clinical standpoint, the most important risk factors for endometriosis are infertility and chronic pelvic pain. In the population of infertile women undergoing surgical evaluation, the rate of endometriosis was higher than in fertile controls and ranged from 4.5 to 33% (mean 14%).[2,5,38,39] Interestingly, the prevalence of infertility among patients with endometriosis has not been precisely evaluated. The etiology of infertility appears clear in women with stage III or IV endometriosis, when periadnexal adhesions and endometriomas distort the anatomy of the fallopian tubes and ovaries. In minimal and mild endometriosis the cause of infertility is less clear, and it may be related to a higher incidence of abnormal oocytes, defective embryos, or failed implantation.[40]

In women with chronic pelvic pain, endometriosis was detected at the time of surgery in 4.5 to 32% (mean 19%).[38,41,42] Typically, pelvic pain consists of dysmenorrhea, intermenstrual pain, and dyspareunia. Dysmenorrhea is the most commonly reported symptom and its severe form, although not entirely predictive, is

highly suggestive of endometriosis.[43] Dyspareunia was found less frequently in ovarian endometriosis (77%) compared with peritoneal (88%) and rectovaginal (100%) forms of the disease.[44] Dysmenorrhea is usually progressive, with onset of pain often preceding the onset of menstrual flow. It usually continues throughout the menses and occasionally persists for several days afterward. The pain is most often localized in the low abdomen and deep pelvis; it is bilateral, often radiating to the back and thighs. It is often described as dull and aching and may be associated with rectal pressure, nausea, and episodes of diarrhea.[45] Intermenstrual pain may represent an extension of dysmenorrhea; in severe cases, patients may suffer from pain throughout the menstrual cycle. Intermenstrual pain has been reported in 57 to 68% of women with endometriosis and pain.[44] In the absence of a cyclic component, this pain may be due to conditions other than endometriosis.[46]

Endometriosis-related dyspareunia is usually positional and most intense upon deep penetration. It is most intense prior to menstruation, but in severe cases it may preclude vaginal intercourse throughout the month. Dyspareunia is usually associated with endometriosis of the cul-de-sac and rectovaginal septum.[47] Interestingly, dysmenorrhea and dyspareunia are more suggestive of endometriosis if the symptoms begin after years of relatively pain-free menses and coitus.[48]

The relationship between pain and the stage and site of endometriosis is controversial. Subjects with advanced disease may have little discomfort, whereas women with minimal or mild endometriosis may present with incapacitating pain. Some reports show a correlation between the severity of dysmenorrhea and the stage of endometriosis.[48,49] Yet, observations to the contrary, revealing no association between the stage of endometriosis and the severity of dysmenorrhea as well as nonmenstrual pelvic pain, have also been published.[44,47,50] Perper et al[51] observed that the intensity of dysmenorrhea was related to the number of endometrial implants but not to the stage of the disease. However, this finding was contradicted by Muzii et al,[49] who reported a lack of correlation between pain severity and the number as well as the type (typical "black" and atypical "fresh/clear") of endometriotic lesions. Evidence regarding the association between the intensity of pain and morphologic features of the endometriotic implants is inconclusive and contradictory.[44,49,52–54] Some data indicate that endometriosis-associated pain persists throughout the reproductive years and that endometriosis stage is directly related to the persistence of pain.[55] Furthermore, deeply infiltrating endometriosis is strongly correlated with pelvic pain and the degree of pain is related to the depth and the volume of infiltration.[47,56,57] In a multicenter cross-sectional observational study of 469 women with surgically diagnosed endometriosis and pain symptoms (>6 months), rectovaginal septum endometriosis was associated with more frequent dyspareunia; however, the statistical significance of this finding was borderline.[44] The same study found no significant correlation between stage and site of endometriosis and severity of dysmenorrhea, nonmenstrual pain, and dyspareunia.

Rarely, endometriosis may present as acute pelvic pain, typically perimenstrual, and usually in the context of hemoperitoneum and rupture or torsion of endometrioma.[58] Endometriosis has also been found in extrapelvic locations, giving rise to atypical symptoms. Nongynecologic organs most often affected by endometriosis include: the intestinal tract, the urinary tract, surgical scars, the lungs and thorax, peripheral nerves, and the central nervous system. Consequently, patients may present with a wide range of cyclic, menses-aggravated symptoms presumably reflecting cyclic bleeding and inflammation. About 0.1% of women who have undergone cesarean section may present with cyclic superficial pain, worsening when coughing and tensing the abdominal wall, that may resemble symptoms of a postoperative hernia.[59–61] Abdominal wall endometriomas are also found in abdominal scars following gynecologic surgeries and in the perineum after episiotomy. Surprisingly, cases of abdominal wall endometriosis have also been described in patients without previous surgical history.[62]

Women with gastrointestinal involvement may suffer from disturbed bowel function, dyschezia, cyclical hematochezia, or even bowel obstruction.[63–67] Hepatic endometriosis may present with cyclic right-sided subcostal pain.[68] Endometriosis of the urinary tract can cause hematuria, dysuria, urgency, and frequency. Bladder detrusor endometriosis presents with symptoms similar to those of interstitial cystitis, whereas renal involvement, although very rare, presents predominantly with abdominal pain and hematuria.[22,69–71] Involvement of the ureter may cause flank and iliac fossa pain due to partial or complete ureteric stenosis. Interestingly, ureteral endometriosis was found in 4.4% of patients with rectovaginal endometriosis.[72] Pulmonary and pleural endometriosis may be manifested by hemoptysis, chest pain, and shortness of breath resembling pulmonary embolism.[73–76] Women with diaphragmatic endometriosis may present with a wide spectrum of symptoms including chronic, cyclical shoulder tip pain.[77,78] Invasion of peripheral nerves can mimic common musculoskeletal problems and may result in cyclic pain such as sciatica, and cerebral endometriosis can lead to perimenstrual headaches or even seizures.[79–83]

Physical Examination

Physical examination may provide a broad range of findings. In some cases, especially of mild endometriosis, the gynecologic examination may be entirely unremarkable. Ideally, the examination should be performed while the patient experiences at least some symptoms, preferably

during menstruation, when it may be easiest to detect and localize areas suspected of harboring endometriosis.[84] A general physical examination is rarely rewarding unless the patient presents with focal cyclic symptoms suggestive of endometriosis in nongynecological organs. Abdominal examination often reveals tenderness, usually ill localized and deep. In rare instances of scar endometriomas, painful swelling and focal tenderness may mimic other lesions, such as hematomas, granulomas, or abscesses.

On pelvic examination, external genitalia and the vaginal surface are usually unremarkable. Speculum inspection may reveal bluish implants typical of endometriosis or red, hypertrophic lesions bleeding on contact, usually in the posterior fornix. In a recent retrospective analysis of 160 cases of histologically documented deeply infiltrative endometriosis, lesions were visible during speculum examination in only 14.4% and palpable during manual examination in 43.1% of patients.[85] Propst et al[86] described a new physical finding of lateral cervical displacement due to scarring of the ipsilateral uterosacral ligament that may be associated with endometriosis. The same group also reported an association between cervical stenosis (<4.5mm) and endometriosis in women with chronic pelvic pain.[87] Most commonly, positive physical signs are found on bimanual and rectovaginal examination of pelvic structures. Palpation of the uterus may reveal retroversion, decreased or absent mobility, and tenderness. Endometriomas may be detected as tender or nontender adnexal masses, often fixed to the uterus or to the pelvic sidewall. Tender masses, nodules, and fibrosis may be appreciated on palpation of the upper vagina, cul-de-sac, uterosacral ligaments, or rectovaginal septum. In a case-controlled study, the only signs of endometriosis in infertile patients were uterosacral nodularity and uterosacral tenderness.[88] Focal tenderness has been shown to correlate with the presence of endometriosis as well as the depth and volume of endometrial implants.[89] Koninckx and his associates[84] found that careful palpation during menstruation increases the detection rate of deep endometriosis, endometriomas, and cul-de-sac adhesions by over fivefold compared with a routine examination not timed to the menstruation.

However, a normal clinical examination does not rule out the diagnosis of endometriosis. When compared with surgical evaluation, pelvic examination showed poor sensitivity, specificity, and predictive values (Table 1). A prospective study validating nonsurgical approaches to diagnosis of endometriosis found that pelvic examination was a reliable predictor of ovarian endometriomas but was not helpful in prediction of nonovarian lesions.[90]

It is essential to bear in mind that the physical signs listed here are not specific and none of the findings is diagnostic in and of itself of endometriosis. Caution should be exercised, and in the absence of conclusive evidence to the contrary, a differential diagnosis should include other conditions such as neoplasms or infections.

LABORATORY TESTS

Multiple attempts have been made to identify serum markers that would serve as reliable screening tests for endometriosis. However, to date, none of the evaluated serum proteins, including CA-125, has adequate sensitivity and specificity to function as a screening tool. At present, there is limited evidence supporting selective use of laboratory tests for therapy follow-up and monitoring of endometriosis recurrence in selected populations at risk.

CA-125

CA-125 is the cell surface antigen expressed by derivatives of coelomic and müllerian epithelia, including endocervix, endometrium, fallopian tube, peritoneum, pleura, and pericardium. This antigenic determinant of high-molecular-weight glycoprotein is detected by monoclonal antibody OC-125. In the mid-1990s a second-generation CA-125 assay of greater precision at low concentrations and reduced variability was introduced. In the CA-125 II assay, the M11 murine monoclonal antibody is used as the capture antibody, followed by labeled OC-125 tracer antibody. Originally, the increased serum levels of CA-125 were detected in patients with invasive epithelial ovarian cancer. However, elevated CA-125 levels have also been observed in serum, menstrual effluent, and the peritoneal fluid of women with endometriosis.[91–97]

Although CA-125 is often elevated in advanced endometriosis, the low sensitivity of this assay limits its usefulness in the detection of minimal and mild disease. Several studies performed in populations at high risk for endometriosis have demonstrated that serum CA-125 has good specificity (86–100%) but poor sensitivity (as low as 13%; Table 2).[177] Sensitivity was improved with the introduction of the new CA-125 II assay as well as other assay modifications.[97,98] The combination of elevated serum CA-125 with positive clinical findings (detection of pelvic nodularities) further improved the diagnostic power of this test, achieving a sensitivity of 87%.[84]

In a meta-analysis of 23 studies (1986–1997) comparing serum CA-125 levels and laparoscopically confirmed endometriosis, the estimated summary receiver operating curve (ROC) revealed a poor diagnostic performance of this test.[99] For example, for a specificity of 90% the sensitivity was only 28%, and the improvement of sensitivity to 50% resulted in a drop in specificity to 72%. CA-125 measurement was a better screening test for diagnosis of moderate to severe endometriosis (stages III and IV). For a specificity of 89% the estimated summary ROC curve showed a sensitivity of 47%, and the

Table 1 Reliability of Pelvic Examination in Diagnosis of Endometriosis

Reference (*n* = Number of Patients)	Finding/Location	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Ripps et al, 1992[89] (*n* = 94)	Focal pelvic tenderness (overall)	79	32	65	50
	Uterosacral ligaments	56–58	72–80	54–62	60–64
	Cul-de-sac	37	97	87	70
	Adnexa	38–43	72–80	54–62	60–64
Koninckx et al, 1996[84] (*n* = 140 and **n* = 55)	Pelvic induration and/or nodularities	36			
	Pelvic induration and/or nodularities at menstruation (overall)*	79	92		
	Deep endometriosis*	77	76	88	
	Endometrioma*	78	70		
	Severe cul-de-sac*	92	77		
Eskenazi et al, 2001[90] (*n* = 90)	Pelvic induration and/or nodularities of uterosacral ligaments/cul-de-sac and/or fixed adnexal mass, fixed uterus and/or vaginal endometriotic lesion	76	74	67	81
Chapron et al, 2002[85] (*n* = 160)	Painful pelvic induration and/or nodularities (overall)	90			
	Bladder endometriosis	73			
	Uterosacral ligaments	83			
	Vaginal endometriosis	100			
	Intestinal endometriosis	94			

increase in sensitivity to 60% was associated with a drop of specificity to 81%.[99] However, the meta-analysis did not account for the effects of the phase of the menstrual cycle. Studies assessing correlation of the assay with clinical parameters (such as pelvic nodularities) are lacking.

Timing of blood collection for CA-125 in relation to the menstrual cycle significantly affects this test. Both in healthy women and in patients with endometriosis, the highest concentrations of CA-125 were detected during menstruation whereas the lowest levels were

Table 2 Reliability of CA-125 in Diagnosis of Endometriosis (Cutoff Level used 35 IU/mL Unless Stated Otherwise)

Reference (*n* = Number of Patients)	Assay; Timing of Sample Collection	Stage	Sensitivity (%)	Specificity (%)
Barbieri et al, 1986[91] (*n* = 147)	Standard assay; timing of sample collection unknown	All	17	96
		III+IV	54	96
Patton et al, 1986[177] (*n* = 113)	Standard assay; timing of sample collection unknown	All	14	93
		III+IV	18	93
Pittaway and Fayez, 1986[92] (*n* = 414)	Standard assay (cutoff level 30 IU/mL); follicular phase	All	17	93
		III+IV	42	93
Koninckx et al, 1992[94] (*n* = 259)	Standard assay; late luteal phase	All	13	96
		III+IV	31	94
O'Shaughnessy et al, 1993[96] (*n* = 100)	Standard assay; menstrual	All	27	100
		III+IV	67	100
Hornstein et al, 1995[97] (*n* = 123)	Standard assay; early follicular phase	All	16	92
		III+IV	40	92
	CA 125 II assay; early follicular phase	All	23	94
		III+IV	60	94
Medl et al, 1997[114] (*n* = 368)	Standard assay; timing of sample collection unknown	All	36	92
		III+IV	44	86
Chen et al, 1998[107] (*n* = 157)	CA 125 II assay; luteal phase	All	61	88
		III+IV	87	88

encountered during the midfollicular and periovulatory phases.[100,101] Koninckx et al[94] suggested that testing in the late luteal phase or during menstruation may be more reliable than testing in the follicular phase. The same group observed that women with superficial disease have pronounced variations in CA-125 levels, whereas women with deep endometriosis and endometriomas have continuously elevated CA-125 throughout the cycle.[94] Interestingly, a subsequent study indicated that the midfollicular CA-125 may be more reliable than the menstrual or the luteal CA-125 in detecting deep endometriosis and endometriomas.[84] Hornstein et al[95] observed that the sensitivity and specificity of the CA-125 assay were comparable during menstruation and in the midfollicular phase, with CA-125 levels consistently higher during menstruation. The reproducibility of CA-125 serum sampling during consecutive menstrual cycles was assessed in a prospective multicenter study.[102] The reproducibility of the test was good during the midfollicular phase in both controls and endometriosis patients, and the CA-125 concentrations during menstrual phase were not reproducible in patients with endometriosis and did not correlate with the disease severity. This study suggests that the best diagnostic accuracy may be achieved by CA-125 determination during the midfollicular phase. O'Shaughnessy et al[96] proposed using the ratio of menstrual to midfollicular CA-125 concentrations (cutoff at a ratio ≥ 1.5) as a better test predicting endometriosis. However, this observation was not confirmed by Hompes et al,[102] who found that the CA-125 menstrual/midfollicular ratio was not reproducible.

Despite the poor sensitivity, several reports have demonstrated that serum CA-125 level correlates with the severity of endometriosis and may predict the response to medical and surgical treatment.[92,103,104] In infertile women who underwent surgical treatment of endometriosis, persistent postoperative elevation of CA-125 independently predicted a poor prognosis, even after accounting for the stage of endometriosis.[105,106] Yet, Chen et al[107] found that CA-125 was not a reliable marker of the effectiveness of medical therapy and observed persistent endometriosis at laparoscopy performed during danazol treatment, despite a reduction of serum CA-125 to normal levels.

Serum CA-125 may also be helpful in differentiating endometriomas from nonendometriotic benign cysts.[108] In a prospective study, most endometriomas contained very high levels of CA-125 (>10,000 U/mL in 78% of cases) while the contents of blood-filled corpus luteum cysts invariably had lower CA-125 concentrations.[109]

Other Laboratory Markers

The search for a reliable marker for endometriosis has been extended to various proteins either naturally secreted by the endometrium or produced in the course of an immune reaction to endometrial and endometrium-related tissues. Markers evaluated for their diagnostic potential in detection of endometriosis comprised CA-72, CA-15–3, TAG-72, and CA-19–9, all of which demonstrated unacceptably low sensitivity.[110–112] One initially promising marker, a product of late secretory endometrium—placental protein 14 (PP14)—was shown to be elevated in endometriosis and to correlate with the severity of the disease.[113] However the relatively good sensitivity (59%) of PP14 assays in the diagnosis of endometriosis obtained in the original report was not substantiated by further studies. In a prospective study, serum levels of tumor-associated trypsin inhibitor (TATI) were found to be elevated in patients with endometriosis and positive correlation with the stage of endometriosis was described. TATI is not a useful screening test, but it may constitute an adjunct diagnostic tool because its combination with the CA-125 assay showed a sensitivity of 59% in detection of all stages of endometriosis and 89% for stage III/IV.[114] Elevated levels of acute inflammatory phase proteins (C-reactive protein and serum amyloid A) have also been demonstrated in severe endometriosis, but the usefulness of these assays remains to be elucidated.[115]

Despite the early promising observations of elevated serum antiendometrial antibodies in patients with endometriosis,[116,117] subsequent studies have failed to show the difference in the antibodies' concentration using immunofluorescence, hemagglutination, enzyme-linked immunosorbent assays, and protein blotting.[118,119] In addition, the correlation between the levels of antiendometrial antibodies and the severity of the disease is very poor.[118]

IMAGING TECHNIQUES

Selective use of imaging studies may be helpful in identifying patients with endometriosis. Detection of large endometriotic implants and endometriomas may be accomplished by transvaginal ultrasonography and magnetic resonance imaging (MRI). Other techniques, such as computed tomography, while occasionally helpful in localizing lesions, often yield nonspecific findings.

Ultrasound

Ultrasonographic examination is the most common imaging modality used to evaluate women suspected of having endometriosis. Ultrasound is particularly helpful in the evaluation of endometriotic cysts but has a limited role in the diagnosis of adhesions or superficial peritoneal implants.[120] Transvaginal ultrasound should be performed preferably using high-frequency probes (6–7.5 MHz) and with the aid of color Doppler imaging. In selected cases, such as abdominal wall endometriosis and bladder endometriosis, a transabdominal approach may also be useful.[121,122]

Ultrasonographic features of endometriomas are diverse. Usually, they present as cystic structures with diffuse low-level internal echoes (95%) and echogenic wall foci.[123,124] Occasionally, endometriotic cysts may have septations, thickened walls, and wall nodularity. Diagnostic performance of ultrasound in the detection of endometriomas was reported to have up to 92% sensitivity and 99% specificity (Table 3).[178,179] Diagnostic accuracy of ultrasound may be enhanced by color Doppler flow studies. Blood flow in endometriomas is usually pericystic, especially noticeable in the hilar region, and usually visualized in regularly spaced vessels.[125] Kurjak and Kupesic[125] demonstrated excellent results with the application of a scoring system based on clinical parameters, CA-125 levels, and sonographic and color Doppler flow characteristics. However, these observations were not reproduced by others, possibly due to differences in clinical characteristics of the populations studied.[126]

There is also controversy regarding the presence of endometrioma vascularization, reported to range from 31 to 98%.[125,127,128] Alcazar[129] found that in patients with pelvic pain vascularization of ovarian endometriomas is higher and the pulsatility index is lower than in asymptomatic patients. Improvement in diagnostic accuracy may be achieved with the introduction of power Doppler, which allows detection of low-velocity flow.[127]

Dermoid cysts, hemorrhagic cysts, and cystic neoplasms may resemble endometriomas and must be considered in the differential diagnosis.[123,124] The application of three-dimensional ultrasound may allow better visualization of the topography of the surface and internal echoes as well as the vasculature of cystic ovarian tumors. More detailed information obtained with the three-dimensional technique may result in more accurate ultrasound performance and better differentiation of endometriomas from other benign and malignant masses.[130,131]

Transrectal ultrasonography was reported to be a useful tool in the diagnosis of deep infiltrating endometriosis. The use of rectal ultrasound with a 6.5-MHz biplane convex probe had a sensitivity of 97% and 80% and a specificity of 96% and 97% in detection of rectovaginal endometriosis and uterosacral ligament infiltration, respectively, as confirmed by surgery and histopathological findings.[132] Infiltration of the intestinal wall by endometriosis was identified by endoscopic rectal ultrasonography (EUS) using 7.5- and 12-MHz radial probes.[133,134] This technique allows circumferential imaging of the rectum and surrounding areas and had a reportedly positive predictive value of 100% in the detection of rectal wall involvement.

Magnetic Resonance Imaging

MRI is particularly helpful in identification of endometriomas. Occasionally, it may also visualize solid endometriotic implants and adhesions. It is an adjunctive noninvasive examination, useful in a preselected, high-risk population.

Endometrial implants are often small and their signal intensity is variable. They usually express an in-

Table 3 Reliability of Transvaginal Ultrasound in Diagnosis of Endometriomas

Reference (*n* = Number of Patients)	Ultrasound Mode; Indication for Surgery	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
Mais et al, 1993[178] (*n* = 236)	B-mode; infertility, CPP, fibroids, adnexal mass	10	75	99	78	98	
Guerriero et al, 1996[179] (*n* = 118)	B-mode; adnexal mass	33	85	97	94	93	0.84
Alcazar et al, 1997[126] (*n* = 78)	B-mode	33	89	91	84	95	
	B-mode + color Doppler imaging (CDI); adnexal mass		76	89	82	82	
Guerriero et al, 1998[127] (*n* = 170)	B-mode	34	81	96	92	91	0.80
	Color Doppler energy (CDE); adnexal mass		90	97	95	95	0.88
Pascual et al, 2000[128] (*n* = 352)	Color Doppler imaging (CDI); adnexal mass	52	92	95	96	92	
Eskenazi et al, 2001[90] (*n* = 90)	B-mode; adnexal mass, fibroids, CPP, infertility	23	57	98	95	76	0.58

tensity similar to that of normal endometrium—hypointense on TI- and hyperintense on T2-weighted images—but may also be hypo- or hyperintense on both TI- and T2-weighted images. Small endometriotic implants are difficult to visualize.[135,136] Some improvement may be achieved with application of the TI-weighted fat suppression technique.[137] Theoretically, implants may be enhanced using contrast medium (gadolinium); but use of this technique failed to improve sensitivity or specificity of MRI in the detection of endometriosis.[138] MRI may also occasionally be suggestive of dense adhesions in the presence of a distortion of the adjacent bowel and in the absence of a detectable interface between the ovary and the surrounding anatomic structures.[135]

MRI is most useful in identification of endometriomas and it has a sensitivity and specificity comparable to or greater than those of transvaginal ultrasound; however, direct comparisons of MRI with ultrasound in the same population of patients are not available (Table 4). Identification of endometriosis by MRI relies on detection of pigmented hemorrhagic lesions. Endometriomas have a relatively homogeneous high signal intensity on TI-weighted images because of degenerated blood products, including methemoglobin and deoxyhemoglobin. A characteristic feature of an endometrioma is "shading"—hypointense signal on T2-weighted images. High concentrations of iron and protein accumulated in endometriotic cysts result in cross-linking of proteins and a subsequent decrease in T2 relaxation time. Signal characteristics vary according to the age of hemorrhage, and endometriomas may have a mixed spectrum of appearances. Acute hemorrhage may be associated with hypointense TI- and T2-weighted images, whereas old hemorrhage may result in hyperintensity of both TI- and T2-weighted images. A hypointense rim of endometrioma may be due to a fibrotic cyst wall combined with hemosiderin-laden macrophages.[135,136,139,140]

Excellent diagnostic performance of MRI was reported by Togashi et al.[141] A diagnosis of endometrioma was best accomplished not only in the presence of hyperintense TI- and hypointense T2-weighted images but also when multiple hyperintense lesions were observed on TI-weighted images regardless of their signal intensity on T2-weighted images. In addition to using routine imaging, a TI-weighted fat-suppressed image improves diagnostic accuracy.[138,142] Administration of gadolinium-based contrast medium resulted in a variable enhancement of the endometrioma wall and was not helpful in differentiation from other cysts.[138]

Pelvic magnetic resonance may also be useful in monitoring the effects of medical therapy as well as in predicting treatment outcome in patients with endometriomas prior to therapy initiation.[143–145] Furthermore, MRI may be useful in detection of nerve invasion (e.g., sciatic endometriosis) and abdominal wall lesions.[80,81,146]

MRI was reported to be valuable in the diagnosis of extraperitoneal endometriotic lesions, especially in the rectovaginal septum. Kinkel et al[147] described the use of MRI in the identification of subsequently histopathologically demonstrated deep endometriosis. They concluded that MRI was able to detect infiltrations of the uterosacral ligaments on T2-weighted images with 100% sensitivity. MRI was also helpful in the diagnosis of bladder and cul-de-sac endometriosis but had unsatisfactory sensitivity in the detection of rectal lesions.[147] The reliability of MRI in the assessment of deep endo-

Table 4 Reliability of Magnetic Resonance Imaging in Diagnosis of Endometriosis

Reference	Assay	Lesion	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Zawin et al, 1989[136]	T1- and T2-weighted imaging	All lesions	71	82	77	76
Arrive et al, 1989[135]	T1- and T2-weighted imaging	All lesions	64	60	—	—
		Implants	13	60		
		Adhesions	48	60		
		Endometrioma	88	60		
Togashi et al, 1991[141]	T1- and T2-weighted imaging	Endometrioma	90	98	94	97
Sugimura et al, 1993[142]	T1- and T2-weighted imaging	Endometrioma	82	91	90	84
		Implants	11	98	33	90
	T1/T2 and fat-suppressed imaging	Endometrioma	91	94	94	92
		Implants	47	97	64	94
Ha et al, 1994[137]	T1- and T2-weighted imaging	Implants	27	98	93	55
	Fat-suppressed imaging		61	87	83	67

metriosis was achieved with the introduction of new technologies, particularly endocavitary and phased-array coils.[122,147] In rare instances, MRI may be helpful in identification of hepatic and rectal endometriotic lesions.[68,148]

Other Imaging Techniques

Various additional imaging procedures may be occasionally useful in the diagnosis of endometriosis. Computed tomography can detect lesions in pleura, brain, and other uncommon locations.[75,79] Barium enema, especially with double contrast, can demonstrate bowel infiltration.[65,149] If bladder or ureteral involvement is suspected, intravenous pyelography, cystoscopy, or ureteroscopy may be performed.[71,150] However, the findings of these techniques are nonspecific and are usually compatible with other conditions such as various inflammatory processes or neoplasms.

SURGICAL PROCEDURES

Laparoscopic assessment in combination with histological examination of the excised lesions remains the gold standard for diagnosis of endometriosis. Knowledge of the most common locations of endometriosis is required for accurate visual inspection of the pelvic and abdominal cavities. Three different forms of endometriosis must be considered during laparoscopic visualization: peritoneal implants, endometriomas, and deep infiltrating lesions of the rectovaginal septum. An increased awareness of the variations in the appearance of endometriotic lesions has resulted in an almost twofold increase in the diagnosis of endometriosis at laparoscopy.[151]

Peritoneal Implants

Peritoneal implants are most commonly localized in the uterosacral ligaments, cul-de-sac, ovarian fossa, and adjacent pelvic sidewalls. Less frequently, implants can also be found in the upper abdomen as well as on the surface of the bladder and the bowel (predominantly rectum, sigmoid colon, appendix, and cecum).[64,71] Hence careful and close inspection of the entire peritoneal cavity should be performed. Magnification obtained during laparoscopy depends on the distance between the laparoscope and the area inspected; for example, the magnification rate is approximately 3.2 and 1.7 from a distance of 10 and 20 mm, respectively.[152] Magnification allows the recognition of lesions as small as 400 μm for red and 180 μm for clear lesions.[151,153]

The classic peritoneal implant appears as a bluish-black "powder burn" lesion with variable degrees of pigmentation and surrounding fibrosis. Typical dark coloration is the result of hemosiderin deposits from entrapped menstrual debris. However, the majority of peritoneal implants appear as nonpigmented, atypical (subtle) lesions, usually red or white. Jansen and Russell[154] have described the relationship between morphological and histological features of various endometriotic lesions. Lesions that were commonly endometriotic included areas of white opacification (81%), red flame-like lesions (81%), and glandular lesions (67%). Less frequently, histological confirmation of endometriosis was obtained in subovarian adhesions (50%), yellow-brown peritoneal patches (47%), and circular peritoneal defects (45%).[154]

As demonstrated by Nisolle and Donnez,[155] red lesions are highly vascularized and proliferative, usually representing an early stage of endometriosis. In contrast, white lesions contain fibrous tissue and are poorly vascularized. They are metabolically inactive and probably represent healed or latent lesions. Black, pigmented foci represent an advanced stage of the disease and the diagnosis of endometriosis has been histologically confirmed in 76 to 93% of these specimens.[156,157] Biochemical activity and clinical features of various lesions from infertile patients with minimal or mild endometriosis were assessed in a prospective study. White peritoneal implants were associated with less pain than black or red lesions, and both black and red lesions showed similar activity expressed in terms of prostaglandin $F_{2\alpha}$ production.[54] In a prospective study, changing patterns in activity of the peritoneal lesions were observed with no change in the stage of the disease when evaluated at laparoscopy before and 6 months after medical therapy.[158]

Redwine[159] proposed that endometrial peritoneal implants undergo a process of "natural evolution." This concept is supported by the observation that the frequency of red lesions and clear papules declines with patients' age and these implants appear to be replaced by black, and ultimately white, scarred lesions over a period of 7 to 10 years.[159] There is a significant overlap in the time course of the presentation of these defects, and all types of lesions may coexist in the same patient.

Endometriosis may also be detected in the lesions visible only under the microscope or scanning electron microscope.[152,160] The prevalence of endometriosis (including microscopic forms) in asymptomatic patients undergoing laparoscopy was estimated to be as high as 45 to 50%.[161] Novel techniques such as "peritoneal blood painting" and infusion of crystalloid into the cul-de-sac ("bubble test") were developed to improve the detection of subtle lesions.[162,163] However, the clinical significance of microscopic endometriosis remains uncertain. It is conceivable that microscopic endometriosis may be present in the majority of women and that a symptomatic disease may develop only in some.[161]

Because endometriotic implants vary in appearance, the experience and the expertise of the surgeon may greatly influence the selection of the biopsy area and hence the likelihood of a diagnosis of endometriosis. In

a prospective study, Walter et al[164] correlated visual diagnosis of endometriosis at laparoscopy with final histological confirmation in 44 patients evaluated for chronic pelvic pain. Use of strict histological criteria resulted in lower rates of confirmed endometriosis because visually detected endometriosis was observed in 36% of cases but confirmed histologically in only 18% of cases.

Peritoneal endometriosis can be associated with other pathological changes such as general hypervascularization and adhesion formation. Adhesions should be evaluated for density (filmy, vascular, dense/fibrotic) and for the extent to which they limit mobility of pelvic organs. Assessment of the severity of periadnexal adhesions is of particular importance in infertile patients because the extent of adhesions is related to the prognosis.[165]

Endometriomas

At the time of laparoscopy, endometriomas may be identified as smooth-walled, dark, brownish cysts, usually strongly associated with the presence of adhesions.[56] Upon incision, dense, brown, chocolate-like fluid is released. As reported by Vercellini et al,[166] careful visual inspection of the ovaries is usually highly reliable in identification of endometriomas, with 97% sensitivity and 95% specificity. Endometriomas larger than 3 cm are frequently multilocular, and in 8% a combination with communicating or noncommunicating luteal cysts has been described.[167]

In patients with enlarged ovaries and at high risk for endometriosis, ovarian punctures may aid in the detection of small and deep endometriomas. Candiani et al[168] found endometriotic material in 48% of aspirates collected from infertile patients who had enlarged ovaries with smooth whitish surfaces and no obvious dominant cysts.

Superficial or deep ovarian endometriosis is a marker for the presence of more extensive disease. Using a computerized pelvic mapping system in 1785 patients with endometriosis Redwine[169] demonstrated that patients with ovarian endometriosis have more pelvic and intestinal areas affected than subjects with no ovarian involvement.

Deep Infiltrating Implants

Deep nodular endometriosis is usually localized in the rectovaginal and uterovesical septum, in other fibromuscular pelvic structures (e.g., uterosacral ligaments), and in the muscular wall of pelvic structures.[170] Rectovaginal nodules are histologically similar to an adenomyoma, being composed of smooth muscle, endometrial glands, and stroma. They probably constitute an entity distinct from peritoneal and ovarian endometriosis and are thought to originate from the müllerian rests present in the rectovaginal septum.[155,171]

Deep endometriotic lesions may be predominantly retroperitoneal with little or no superficial peritoneal involvement. These lesions, associated with pain and infertility, have been classified as deep when infiltrating more than 5 mm beneath the peritoneal surface.[172,173] Evaluation of the size and the depth of the nodule may be difficult at laparoscopic examination; however, meticulous palpation using a probe may identify these lesions. A subtle retraction of the bowel may also be suggestive of deep implants. Identification of deep endometriosis is greatly improved by a careful preoperative examination, preferably during menstruation, of the posterior vagina, cul-de-sac, and uterosacral ligaments.[84]

Abdominal Wall Endometriosis

When endometrioma in a surgical scar is suspected, histopathological diagnosis can be obtained by a fine-needle aspiration biopsy.[174]

Transvaginal Hydrolaparoscopy

Transvaginal hydrolaparoscopy, using a needle-cannula system inserted into the posterior fornix and injection of saline for peritoneal distention, was recently introduced as an office screening technique for infertile women. Interestingly, it was reportedly more accurate than traditional laparoscopy in diagnosis of early endometriotic lesions.[175,176]

CONCLUSIONS

Diagnosis of endometriosis remains challenging. Despite an extensive search for new laboratory tests and advances in imaging technologies, at present there are no simple noninvasive diagnostic tests. Complete clinical assessment supported by selective and critical use of laboratory and imaging studies can help in the identification of a high-risk patient population. However, in a large proportion of cases, diagnosis of endometriosis requires careful laparoscopic evaluation combined with a thoughtful interpretation of histological examination of excised lesions. Misdiagnoses and underdiagnoses of endometriosis are due not only to the limitations of diagnostic tools but also to a lack of recognition of the symptoms by the patients and physicians. Although in a large proportion of patients, early diagnosis of endometriosis is essential for the formulation of an appropriate treatment plan, one should keep in mind that detection of endometriosis in asymptomatic women does not automatically necessitate medical or surgical intervention.

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