Special Report

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Women's Health

Problems with the diagnosis of endometriosis

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Endometriosis is classically defined as the presence of endometrial glands and stroma in outside the uterine cavity. As the definition suggests that confirming the ectopic endometrial stroma and glands in ectopic location histopathologically should be necessary for the diagnosis of endometriosis. Therefore, this situation leads to the need for surgery like laparoscopy for diagnosis. However, this surgical diagnostic approach will not be reliable for all patients with suspected endometriosis. It seems to be an important problem that there is still no reliable clinically diagnostic method or pathognomonic clinical finding, which may allow accurate diagnosis of endometriosis without the need for surgery or histopathologic evaluation. While these clinical features are not pathognomonic for the endometriosis, they should be used as markers for creating high-risk population for endometriosis. Clinical features and the available diagnostic methods, their advantages and limitations for the endometriosis will be discussed in this article. The different options for clinical assessment, laboratory tests and imaging techniques will be summarized and the advantages and disadvantages of these methods will be evaluated. We will also discuss the gold standard definitive diagnostic options with their problematic aspects.

Keywords: CA-125 • chronic pelvic pain • dysmenorrhea • dyspareunia • endometrioma • endometriosis • endometriotic implants • infertility • laparoscopy

Clinical assessment

History

Diagnosis of endometriosis on the basis of symptoms alone can be difficult because the presentation is so variable and there is no pathognomonic symptom for endometriosis in clinical presentation. Different types and stages of pain are the most common symptoms that patients complain in endometriosis. Approximately three quarters of symptomatic patients experience pelvic pain in different types such as chronic pelvic pain, dysmenorrhea, dyspareunia, lower back pain. Infertility, abnormal menstrual bleeding are the other nonspecific gynecologic symptoms of endometriosis [1]. In addition, endometriosis has also been found in nongynecologic organs and extrapelvic locations such as gastrointestinal tract, the urinary tract, surgical scars, the lungs and thorax, peripheral nerves and the CNS. This condition may cause atypical cyclic symptoms and may result more problematic consequences for the differential diagnosis of endometriosis.

The predictive value of any symptom remains uncertain as each of these symptoms can have other causes. Furthermore, a significant proportion of affected women are asymptomatic. A complete history with the identification of symptoms highly suggestive for endometriosis may be important to determine a high-risk group for endometriosis. Thus, only the high-risk population will conducted for detailed diagnostic procedures. In addition, the identification of the high-risk population will increase the specificity and sensitivity of the subsequent diagnostic tests of endometriosis.

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Physical findings

Physical examination findings in women with endometriosis are quite variable as well as symptoms. Furthermore, there are usually no abnormal signs on the physical examination especially for the mild endometriosis cases [2]. Even if the findings are present, they are generally not specific to the endometriosis. The most common finding that brings to mind endometriosis is tenderness on the palpation of the posterior fornix. Palpable endometriotic lesions may be visible with speculum examination in the posterior fornix in deep endometriosis.

Thickening and induration of uterosacral ligaments, pain with uterine movement, enlarged adnexal masses and fixation of adnexa or uterus in a retroverted position, cervical displacement due to scarring of the ipsilateral uterosacral ligament and cervical stenosis are the other common gynecologic findings that may be strongly associated with endometriosis in patients [3,4]. These findings that are associated with endometriosis may also occur in different gynecologic situations such as pelvic inflammatory diseases, abscess and hematomas.

It is suggested that the physical examination should be performed, while the patients are symptomatic or during menstrual period for detecting the suspected areas of endometriosis [5]. Positive physical signs are found better on bimanual and rectovaginal examination of pelvic structures. Pelvic examination has a poor sensitivity and specificity compared with surgical approach [6]. A normal physical examination *per se* does not rule out the diagnosis of endometriosis.

Biochemical markers

It has been investigated many times to identify any biochemical marker with high sensitivity and specificity for diagnosis or screening the endometriosis. Unfortunately, there is still no biochemical marker that has adequate sensitivity and specificity to screen the disease. Several markers will be discussed in the section.

CA-125

CA-125 is a cell surface antigen expressed by derivatives of coelomic and mullerian epithelia. Various different pathologies associated with tissues that covered with coelomic and mullerian epithelia such as endocervix, endometrium, fallopian tube, peritoneum, pleura and pericardium may cause increased serum CA-125 levels. Therefore, increased serum levels of CA-125 were not detected only in patients with endometriosis [7].

The sensitivity and specificity of the CA-125 is higher in moderate or severe endometriosis (stage III or IV) [8]. However, low sensitivity of this assay limits its usefulness in the detection of minimal endometriosis. Several studies performed in populations at high risk for endometriosis have demonstrated that serum CA-125 had good specificity and sensitivity. It is also well recognized that combination of elevated serum CA-125 with positive clinical findings improved the diagnostic power of the test [5]. Therefore, the test should be evaluated with clinical findings together.

CA-125 levels are higher during menstruation than midfollicular and periovulatory phases in healthy women. The timing of blood sampling for the CA-125 testing is important during the menstrual cycle. There is no consensus about the best timing of the blood sampling for the best diagnostic power. One study evaluating the timing of the blood sampling of CA-125 for the endometriosis suggested that testing in late luteal phase or during menstruation will be more reliable than testing in the midfollicular phase [9]. However, Hornstein *et al.* [10] concluded 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. Furthermore, O'Shaughnessy *et al.* [11] proposed using the ratio of menstrual to midfollicular CA-125 concentrations as a better test in the diagnosis of the endometriosis. However, subsequent studies did not confirm the reliability of ratio as a useful diagnostic tool [12].

Although CA-125 level was not the exact indicator for the severity of the endometriosis, it may provide useful information about the severity of the disease. Persistent postoperative elevation of CA-125 is a good predictor for the poor prognosis in infertile women with endometriosis [13].

Other markers

Some other markers researched for diagnosis of endometriosis such as CA-72, CA 15-3 and CA 19-9, but they have demonstrated unacceptably low sensitivity in the detection of endometriosis [14]. PP14 and TATI are initially promising markers that were shown to be elevated in endometriosis and to be correlated with severity of the disease [15,16]. However, further studies that evaluate these markers one by one or within a combination are required to determine their reliability and to introduce them in routine practice.

HE4 is a promising biomarker for ovarian cancer but not for endometriosis. Thus, it can be useful in the differential diagnosis in patients with endometriosis and pelvic mass [17].

Imaging technics

Transvaginal ultrasound and MRI may be useful for identifying the patients with endometriosis. Endometriomas and some large endometriotic implant can be detected by imaging techniques.

Ultrasound

Ultrasonography, which is usually performed to identify pelvic organ abnormalities, is most common imaging modality used for differential diagnosis of endometriosis. However, its use is limited with evaluation of the endometriotic cysts-endometriomas in general. Frequent features of endometrioma are diffuse low-level internal echogenities, echogenic wall foci, septations, thickened walls and wall nodularity. Ultrasound has a very high sensitivity and specificity rates in the detection of endometriosis (92 and 99%, respectively) [18]. Imaging pericystic, especially noticeable in the hilar region and visualized in regularly spaced vessels by the color Doppler, will enhance diagnostic accuracy. Malign cystic neoplasms, dermoid cysts, hemorrhagic cysts and the other benign conditions should be in the differential diagnosis of the endometriomas. 3D ultrasound may be applicable for visualization of the topography of the surface and internal echoes and may be better choice in the differentiation of endometriomas from other masses. Although its limited use in gynecological practice, transrectal ultrasonography is valuable in the detection of rectovaginal endometriosis and uterosacral ligament infiltration with a high sensitivity and specificity rates.

MRI

MRI is a helpful and noninvasive imaging method that may visualize solid endometriotic implants and adhesions in selected high-risk population. Normal endometrium expresses hypointense on T1 and hyperintense on T2-weighted images. Although endometriotic implants generally express same intensity with normal endometrium, they may also be hypo- or hyper-intense on both T1- and T2-weighted images [19]. Despite to the efforts to improve the image quality like T1-weighted fat suppression technic or using contrast medium, it is difficult to visualize small implants at all [20,21].

MRI may identify endometriomas with a high sensitivity and specificity. Degenerated blood products, including methemoglobin and deoxyhemoglobin, ensure the endometriomas homogeneous high signal intensity on T1-weighted images. However, high concentrations of iron and protein accumulated in endometriotic cysts result in cross-linking of proteins and a subsequent decrease in T2 relaxation time. Thus, in contrast to T1-weighted images endometriomas have hypointense signal on T2-weighted images. Although signal characteristics vary according to the age of hemorrhage, this characteristic feature makes MRI have high diagnostic accuracy.

MRI seems to be an acceptable diagnostic test endometriosis with high diagnostic sensitivity, specificity and accuracy (90, 98 and 96%, respectively) in the literature [22]. MRI was also reported to be valuable in the diagnosis of deep endometriosis of uterosacral ligaments, the bladder and the pouch of Douglas.

Surgical procedures

Laparoscopic exploration with a combination histopathological examination of the suspected implants is the gold standard of the diagnosis of endometriosis. Endometriotic implants should be searched in pelvis especially on uterosacral ligaments, cul-de-sac, ovarian fossa, pelvic sidewalls, surface of the bladder and the bowel (rectum, sigmoid colon, appendix and cecum). Magnification feature of laparoscopy has significant superiority to laparotomy in the inspection of the abdomen for small endometriotic implants [23].

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.

Another important problem in the process of the diagnosis is the variability of the peritoneal implants. The morphologic characteristics and clinical importance of nonpigmented peritoneal lesions that have the histologic features of endometriosis have been described by Jansen and Russell in a study, which was evaluate 137 laparoscopic biopsy specimens [24]. They reported nonpigmented lesion types that were commonly endometriotic as white opacification (81%), red flame-like lesions (81%) and glandular lesions (67%). Subovarian adhesions (50%), yellow–brown peritoneal patches (47%) and circular peritoneal defects (45%) thickened cribriform peritoneum (9%) were noted not common endometriotic in their study.

It is reported that very small or visually normal lesions including microscopic forms that do not cause any abnormality on the peritoneal surface may be exist as well as the visible endometriotic implants in the literature. Although most of these lesions are known to be asymptomatic, they were been associated with some symptoms like chronic pelvic pain and unexplained infertility previously [25]. There have been some methods defined like 'peritoneal blood painting, bubble test' to determine the endometriotic lesions those were directly unvisualized by laparoscopy, however, it should be questioned the necessity of diagnosing such lesions that have uncertain clinical significance [26,27].

Having a final decision about the endometriotic implants only with the laparoscopic view may cause some problems in the differential diagnosis of endometriosis. In a prospective study that purposed to

correlate the diagnosis of endometriosis on the basis of visualization at laparoscopy with the pathologic diagnosis found that the mean prevalence of abnormalities visually consistent with endometriosis was 36%, with 18% confirmed histologically [28]. In addition, the positive predictive value, sensitivity, negative predictive value and specificity were found 45, 97, 99 and 77%, respectively, for visual versus histologic diagnosis of endometriosis, and 26% of the diagnoses of endometriosis were downstaged on the basis of histologic findings in the same study. This study indicates that diagnosis of endometriosis should be established after histopathologic confirmation due to variety of the endometriotic implants and the experience and expertise of the surgeons may influence the selection of the biopsy area.

Endometriomas can be recognized with smooth-walled, dark brownish color and dense adhesions to the surrounding tissues at the time of laparoscopy. The most important indicator that allows the correct diagnosis in the surgery is the dense, brown, chocolate-like fluid of the cysts. Vercellini *et al.* [29] reported that visual detection of endometriomas is remarkably accurate with a sensitivity of 97%, specificity of 95%, positive and negative predictive value of 98 and 94%, respectively, and overall accuracy of 96%. Ovarian biopsy, although desirable in some cases, would seem dispensable for a correct laparoscopic diagnosis for endometriomas.

Conclusion

Diagnosis of endometriosis is already a problematic process in gynecologic practice. Extensive search for new laboratory tests and advances in imaging technologies promise new diagnostic tools in near future.For example, endometrial nerve fibers have investigated recently for the diagnosis of endometriosis. It was confirmed that the validity of the detection of endometrial nerve fibers, using immunohistochemical techniques on an endometrial biopsy, as a diagnostic test has a high level of sensitivity and specificity [30]. However, laparoscopic exploration with a combination histopathological examination of the suspected implants is the gold standard of the diagnosis of endometriosis. Identification of a high-risk patient population for endometriosis with complete clinical assessment supported by selective use of laboratory and imaging studies and then perform surgery to only these high-risk population will prevent unnecessary surgery.

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Executive summary

- Endometriosisis associated with different types of pelvic pain, infertility and a variety of nonspecific symptoms.
- The most common finding of endometriosis is tenderness on the palpation of the posterior fornix.
- CA-125 is valuable marker for endometriosis especially for moderate or severe endometriosis.
- Endometriomas and some large endometriotic implant can be detected by imaging techniques.
- Laparoscopic exploration with a combination histopatological examination of the suspected implants is the gold standard of the diagnosis of endometriosis.

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