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Clinical diagnosis of endometriosis: a call to action

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Conflicts of Interest

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Condensation

Long delays common in the diagnosis of endometriosis warrant reconsidering standard practices, historically rooted in surgery, in favor of accessible, expedient, and noninvasive clinical approaches.

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Abstract

Endometriosis can have a profound impact on women's lives, including associated pain, infertility, decreased quality of life, and interference with daily life, relationships, and livelihood. The first step in alleviating these adverse sequelae is to diagnose the underlying condition. For many women, the journey to endometriosis diagnosis is long and fraught with barriers and misdiagnoses. Inherent challenges include a gold standard based on an invasive surgical procedure (laparoscopy) and diverse symptomatology, contributing to the well-established delay of 4 to 11 years from first symptom onset to surgical diagnosis. We believe remedying the diagnostic delay requires increased patient education and timely referral to a women's healthcare provider and a shift in physician approach to the disorder. Endometriosis should be approached as a chronic, systemic, inflammatory and heterogeneous disease that presents with symptoms of pelvic pain and/or infertility rather than focusing primarily on surgical findings and pelvic lesions. Using this approach, symptoms, signs, and clinical findings of endometriosis are anticipated to become main drivers of clinical diagnosis and earlier intervention. Combining these factors into a practical algorithm is expected to simplify endometriosis diagnosis and make the process accessible to more clinicians and patients, culminating in earlier effective management. The time has come to bridge disparities and minimize delays in endometriosis diagnosis and treatment for the benefit of women worldwide.

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The Problem: Endometriosis is undiagnosed in a large proportion of affected women, resulting in ongoing and progressive symptoms with associated negative impacts on health and well-being. Current practice standards, which rely primarily on laparoscopy for a definitive diagnosis before beginning therapy, frequently result in prolonged delay between symptom onset, diagnosis, and subsequent treatment.

A Solution: Enhanced utilization of clinical diagnostic techniques may reduce the delay in time to diagnosis and, hence, bring more rapid relief to affected patients, limit disease progression, and prevent sequelae.

Introduction

Endometriosis has such wide-ranging and pervasive sequelae that it has been described as “nothing short of a public health emergency” requiring immediate action.[1] Population-based data suggest more than 4 million reproductive-age women have diagnosed endometriosis in the United States.[2] As daunting as this number is, it only tells part of the story, as an estimated 6 of 10 endometriosis cases are undiagnosed.[3] Thus more than 6 million American women may experience repercussions of endometriosis without benefit of understanding the cause of their symptoms or appropriate management.

When discussing the patient’s experience with endometriosis, pain and infertility are usually of greatest concern, as they are two of the disease’s more common symptoms. But the real toll is even greater; women with endometriosis experience diminished quality of life, increased incidence of depression, adverse effects on intimate relationships, limitations on participation in daily activities, reduced social activity, loss of productivity and associated income, increased risk for chronic disease, and significant direct and indirect healthcare costs.[4-8] Moreover, emerging data indicate endometriosis is associated with greater risk for obstetric and neonatal complications.[9-12]

The challenge of diagnosing endometriosis

There are no pathognomonic features or biomarkers necessary and sufficient to define endometriosis. Rather, key symptoms that currently prompt surgical evaluation, such as pain and infertility, can have multiple causes. Endometriosis is typically defined by its histology: extrauterine lesions consisting of endometrial glands, endometrial stroma, and/or hemosiderin-laden macrophages. Based on location and depth, lesions are further described as superficial

peritoneal lesions, ovarian endometrioma, or deep endometriosis. However, the presence of lesions does not preclude other etiologies for the patient's symptoms, and the lack of obvious lesions does not eliminate the possibility of endometriosis. Furthermore, there is poor correlation between symptoms and severity or extent of disease, as quantified by current staging systems.[13] From a clinical perspective, endometriosis may be better defined as a menstrual cycle dependent, chronic, inflammatory, systemic disease that commonly presents as pelvic pain. Moving from a histological to a clinical definition opens the door to a different approach to diagnosis, one that emphasizes symptoms and their origins over lesion presence or absence, and that may, in future, be validated by specific, noninvasive disease biomarkers.

Among those who ultimately receive a successful definitive diagnosis, contemporary literature describes delays from symptom onset to diagnosis ranging from 4 to 11 years.[5, 14-18] Several factors exacerbate this delay,[14, 15, 17, 18] including "normalization" of symptoms and misdiagnosis.[15] The presence of diagnostic delays is a worldwide phenomenon, occurring even in countries with universal healthcare.[15, 17] Consequences of the delay in diagnosis are experienced by patients in multiple ways, including persistent symptoms and a commensurate detrimental impact on quality of life,[14] erosion of the patient-physician relationship,[4, 5] and development of central sensitization—a mechanism whereby persistent endometriosis-associated pain increases pain awareness, even at sites unconnected anatomically with the lesion(s).[14, 19-21] Moreover, although the evidence is limited, failure of timely diagnosis and adequate endometriosis management may foster disease progression and adhesion formation that may compromise fertility and increase the risk for central sensitization and chronic pelvic pain.[22-24]

The current diagnostic paradigm, endorsed by professional societies, requires laparoscopy with or without histologic verification as the gold standard, although many societies endorse the treatment of symptoms before obtaining a definitive surgical diagnosis.[25-29] Notably, the 2017 National Institute for Health and Care Excellence guidelines reflect a philosophical shift, presenting empiric therapy prior to laparoscopy in the diagnostic and treatment algorithm unless fertility is a priority.[30] Although the merits of laparoscopy and its role in disease management should not be minimized, its accuracy, risks, and cost-effectiveness warrant reevaluation. The poor correlation between reported symptoms and extent of disease found at laparoscopy further illustrates the limitations of surgical disease assessment.[31] Detecting endometriosis via laparoscopy relies on lesions' visual identification, a practice that is challenged by heterogeneous lesion appearance,[32] inaccessible lesion location (particularly for deep lesions),[33] and interobserver variability.[34] Surgical risks associated with laparoscopy are generally low,[33, 35] although they merit consideration given the potential for major complications (albeit rare)[36] and need for retreatment after initial laparoscopy because there is no surgical cure for endometriosis.[37] From a pragmatic perspective, evaluation of laparoscopy for endometriosis diagnosis and management must include a discussion of costs, which are substantially higher compared with nonsurgical approaches.[38]

Argument for clinical diagnosis

Reliance on laparoscopy for endometriosis diagnosis supports the viewpoint that the presence of identifiable lesions in the pelvis is the central tenet of endometriosis, rather than approaching endometriosis as a menstrual cycle dependent, chronic, inflammatory, systemic disease that often presents as pelvic pain. By shifting the paradigm to the patient rather than

the lesion, the path to clinical diagnosis has the potential to be more inclusive with reduced diagnostic delay. Indeed, Soliman et al[18] reported diagnosing endometriosis by nonsurgical methods shortened the mean time from first consultation to diagnosis compared with surgical diagnosis. This shift, however, requires clinical diagnostic methodologies that accurately identify endometriosis. To that end, we have compiled data on the accuracy of clinical assessments for diagnosing endometriosis (Table1). Notably, these studies were highly heterogeneous, which precluded performance of a meaningful meta-analysis.

Symptoms

Pelvic pain, although common among women with endometriosis, is insufficient alone as an indicator of endometriosis, as it can be associated with several gynecologic (and nongynecologic) conditions.[39] However, pelvic pain that is described as chronic, cyclic, and persistent or progressive (ie, worsening over time) increases the likelihood of an association with endometriosis.[2, 40, 41] Pain is typically initially menstrual (dysmenorrhea), but may progress to include nonmenstrual pelvic pain, which is prevalent among women with diagnosed endometriosis.[42] When asked about their experiences living with endometriosis, participants in the qualitative study by Moradi et al[5] universally described their pain as “severe and progressive during menstrual and nonmenstrual phases.” Women with endometriosis are more likely to report dyspareunia, dyschezia, and dysuria than unaffected women.[2, 40, 43-46] Although the sensitivity of dyspareunia is generally low,[47-49] indicating that its presence is not specific to endometriosis, deep dyspareunia is associated with deep endometriosis.[46]

Response of pain to treatment may be another indicator of endometriosis. Whereas nonsteroidal anti-inflammatory drugs (NSAIDs) effectively treat primary dysmenorrhea, pain reduction with these agents may be insufficient in women with endometriosis.[26, 28] However,

caution is indicated before dismissing NSAID-responsive pain as simply dysmenorrhea; early symptoms of endometriosis may be responsive to these agents, and we should not miss an opportunity to treat the disease before the development of serious sequelae.

Patient and family history

History of infertility is strongly associated with endometriosis, although this may be skewed due to more thorough evaluation of women with infertility increasing the chances of successful diagnosis.[2, 41, 43-47] Other factors associated with a greater likelihood of successful endometriosis diagnosis are family history of the disease,[43, 50] previous pelvic surgery,[50] and a history of benign ovarian cysts and/or ovarian pain.[43, 45]

Menstrual cycle characteristics

In a recent cross-sectional survey of approximately 50,000 women, several menstrual cycle characteristics were more prevalent among women with vs. without diagnosed endometriosis, including heavy menstrual bleeding, excessive/irregular bleeding, passing clots, and irregular periods. Premenstrual spotting also correlates with endometriosis in infertile women.[48, 50] While these disorders are common in women with endometriosis, most have regular cycles without abnormal bleeding.

Physical examination

Data from comparative studies suggest findings on physical examination can identify endometriosis with high accuracy.[51-53] For example, using defined criteria for a positive bimanual pelvic examination (ie, palpable nodularity, stiffened and/or thickened pelvic anatomy, especially the uterosacral ligaments, vagina, rectovaginal space, pouch of Douglas, adnexa, rectosigmoid, or posterior wall of the urinary bladder), Hudelist et al[51] reported

endometriosis diagnosis accuracy of 86% to 99%, depending on anatomic location. Diagnostic acumen of pelvic examination is lower for deep endometriosis,[52, 53] although examination during menses improves detection.[26] Anterior vaginal wall tenderness has low sensitivity for detecting endometriosis in women with chronic pelvic pain,[54] but demonstrates prognostic value for endometriosis among women with unexplained infertility.[55] A caveat to bimanual examination is that it may not be feasible for non-sexually active adolescents/young adults and may not identify early-stage, superficial disease.

Combination assessments

The ability to identify endometriosis nonsurgically is enhanced when multiple factors are combined. Ballard et al[45] reported that the likelihood of endometriosis increased with the number of symptoms present, from an odds ratio of 5.0 with 1 symptom to 84.7 for 7 or more symptoms. Several investigators have utilized this approach to develop models for predicting endometriosis.[43, 46, 56] Using data from a prospective, multinational study, Nnoaham et al[43] created a model combining symptoms and patient history with ultrasound findings that predicted revised American Society for Reproductive Medicine (rASRM) stage III and IV endometriosis with good accuracy. The authors suggest that such screening tools could reduce “diagnostic delay, high investigation costs, and personal suffering associated with endometriosis.”[43]

Additional considerations

Imaging can be a useful adjunct to clinical diagnostic measures, and transvaginal ultrasound improves accuracy when used adjunctively with symptoms, patient history, and/or physical findings.[43, 49, 51] Ultrasound is particularly sensitive for detecting ovarian endometriomas and deep endometriosis.[25, 57, 58] Indeed, a Cochrane meta-analysis found that

transvaginal ultrasound approaches the sensitivity and specificity needed to replace surgery for endometrioma detection.[57] The International Deep Endometriosis Analysis (IDEA) group consensus statement on systematic sonographic evaluation of the pelvis in women with suspected endometriosis provides standards for improved imaging.[59] Traditional routine transvaginal ultrasound may be limited to endometrioma diagnosis; however, “expert-guided” imaging, as outlined by the IDEA group, will help improve clinical assessment across endometriosis manifestations. Nonetheless, not all endometriosis will be visualized by imaging and imaging cannot be used to rule-out endometriosis.

Magnetic resonance imaging is a noninvasive option; however, it is expensive, not universally available, and lacks sensitivity and is, therefore, infrequently used for endometriosis diagnosis. Although many are currently being studied, as yet, no noninvasive or minimally invasive biomarker has been established to diagnose endometriosis.[60-62]

Much of what is known about endometriosis comes from surgically diagnosed adults. Increased research into endometriosis among surgically diagnosed adolescents and prospective studies of those with suggestive signs and symptoms will help to better identify hallmarks of disease onset and risk factors for disease progression and treatment prognosis. While a detailed review of endometriosis in adolescents is beyond the scope of this discussion, it is noteworthy that endometriosis occurs in adolescents and that patients who are younger at the time of symptom onset experience longer diagnostic delays than older patients.[17, 18] This delay is attributed to prolonged time before seeking treatment and a longer interval between first clinical consultation and referral or diagnosis. It is important that clinicians evaluate symptoms that merit suspicion in adolescents as seriously as in adults.[42]

Implementing Clinical Diagnosis

Clinical diagnosis is already applied in clinical practice, albeit inconsistently and without standization.[2, 18] In an effort to provide a unified, practical approach to clinically diagnosing endometriosis, we have developed an algorithm informed by evidence in the literature and clinical experience (Figure 1). The proposed algorithm utilizes techniques readily available to most practitioners and allows clinicians to initiate treatment without delay or invasive procedures. For each step, we identify findings that are consistent with endometriosis and those suggesting a possible alternative diagnosis. In general, persistent and/or worsening cyclic or constant pelvic pain, particularly in the presence of other endometriosis-associated symptoms, patient history, and findings on physical examination, suggest endometriosis. When these findings are unclear, imaging with transvaginal ultrasound is a widely available and low-cost option.

This algorithm does not diminish the value of laparoscopy as a treatment option in those for whom medical therapy is insufficient, nor does it minimize laparoscopy as a diagnostic tool when clinical signs are uncertain or suggest nonendometriosis pathology (eg, other benign or malignant ovarian neoplasms). Rather, the algorithm is intended to make the diagnosis of endometriosis more accessible, reducing the negative impact of undiagnosed and untreated endometriosis on women's lives. Practitioners should feel empowered to clinically diagnose this disease early and without an invasive procedure. Although the ramifications of early diagnosis and treatment have not been studied, the potential exists to relieve pain, avoid central sensitization and pain persistence, prevent infertility, and change the trajectory of patients' lives. It is increasingly recognized that chronic diseases such as endometriosis generate cumulative life-course impairment through limitations imposed on life choices,

including education, career, and family.[5, 63] Overall patient health may also be improved by addressing the psychosocial and physical manifestations often found in conjunction with endometriosis, such as persistent pelvic pain, depression, anxiety, fatigue, bloating/weight gain, gastrointestinal issues, and sexual dysfunction.[2, 4, 5, 50] Now is the time to change the paradigm of the diagnosis of endometriosis by increasing speed and validity, leading to improved access to effective early treatment.

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Table 1. Predictive value of signs, symptoms, and clinical findings for diagnosing endometriosis

Study design and population	Method of diagnosis	Assessment or parameter	Results
Endometriosis (General)			
Saha 2017[47]*	Endometriosis diagnosis listed in electronic medical record	Severe dysmenorrhea	Sensitivity: 58%; Specificity: 70%
		Chronic pelvic pain	Sensitivity: 25%; Specificity: 89%
Cross-sectional survey of a Swedish twin cohort (N = 26,898)		Dyspareunia	Sensitivity: 16%; Specificity: 96%
		Infertility	Sensitivity: 28%; Specificity: 93%
		Oral pill as contraceptive	Sensitivity: 16%; Specificity: 80%
Fuldeore 2017[2]	Self-report (Replying in the affirmative that a doctor had previously told the subject that she has or is suspected of having endometriosis)	Menstrual pelvic pain/cramping	OR, 1.6 (95% CI, 1.4-1.8)
		Nonmenstrual pelvic pain/cramping	OR, 4.1 (95% CI, 3.6-4.6)
Respondents to an online, cross-sectional survey (N = 48,020)		Dyspareunia	OR, 3.1 (95% CI, 2.8-3.5)
		Heavy menstrual bleeding	OR, 1.5 (95% CI, 1.3-1.7)
		Excessive or irregular bleeding	OR, 2.1 (95% CI, 1.8-2.4)
		Passage of clots	OR, 1.8 (95% CI, 1.6-2.0)
		Irregular periods (timing/duration)	OR, 1.5 (95% CI, 1.3-1.7)
		Constipation/bloating/diarrhea	OR, 1.9 (95% CI, 1.7-2.2)
		Fatigue/weariness/anemia	OR, 2.2 (95% CI, 2.0-2.5)
		Infertility	OR, 3.6 (95% CI, 3.0-4.4)
Ashrafi 2016[50]	Laparoscopically-	Family history of endometriosis	OR, 2.7 (95% CI, 1.06-7.1)

Table 1. Predictive value of signs, symptoms, and clinical findings for diagnosing endometriosis

Study design and population	Method of diagnosis	Assessment or parameter	Results
	visualized	History of galactorrhea	OR, 1.8 (95% CI, 1.1-3.05)
Retrospective case-control study involving women who underwent laparoscopy for infertility evaluation (341 with endometriosis; 332 with a normal pelvis)	endometriosis	History of pelvic surgery	OR, 14.5 (95% CI, 6.1-34.2)
		Dysmenorrhea	OR, 1.8 (95% CI, 1.1-2.8)
		Pelvic pain	OR, 4.1 (95% CI, 2.4-6.8)
		Dyspareunia	OR, 1.6 (95% CI, 1.09-2.4)
		Premenstrual spotting	OR, 2.2 (95% CI, 1.3-3.6)
		Fatigue	OR, 2.6 (95% CI, 1.3-5.1)
Apostolopoulos 2016[64]	Laparoscopically-visualized endometriosis	Noncyclical pain	Endometriosis: 62.5%; No endometriosis: 70.8%; $p = 0.48$
		Dysmenorrhea	Endometriosis: 79.1%; No endometriosis: 87.5%; $p = 0.37$
		Dyspareunia	Endometriosis: 25.0%; No endometriosis: 33.3%; $p = 0.46$
Prospective, observational study of women who underwent laparoscopy for		Dyschezia	Endometriosis: 25.0%; No endometriosis: 20.8%; $p = 0.69$

Table 1. Predictive value of signs, symptoms, and clinical findings for diagnosing endometriosis

Study design and population	Method of diagnosis	Assessment or parameter	Results
chronic pelvic pain (N = 144)			
Schliep 2015[40] Operative cohort from the ENDO study—women without a history of surgically confirmed endometriosis who underwent laparoscopy or laparotomy (N = 473)	Surgically visualized endometriosis	Chronic pelvic pain	Endometriosis: 44.2%; Other: 39.0%; Normal pelvis: 30.2%; $p = 0.04$
		Cyclic pelvic pain	Endometriosis: 49.5%; Other: 31.0%; Normal pelvis: 33.1%; $p < 0.001$
		Vaginal pain with intercourse	Endometriosis: 54.7%; Other: 41.5%; Normal pelvis: 32.4%; $p < 0.001$
		Deep pain with intercourse	Endometriosis: 53.2%; Other: 38.1%; Normal pelvis: 30.9%; $p < 0.001$
		Burning vaginal pain after intercourse	Endometriosis: 33.2%; Other: 22.5%; Normal pelvis: 22.1%; $p = 0.03$
		Pain just before period	Endometriosis: 75.3%; Other: 61.9%; Normal pelvis: 66.2%; $p = 0.03$
		Level of cramps with period	Endometriosis: 91.1%; Other: 85.0%; Normal pelvis: 79.4%; $p = 0.01$
		Pain after period is over	Endometriosis: 38.4%; Other: 26.5%; Normal pelvis: 38.2%; $p = 0.04$
		Pain at ovulation (mid-cycle)	Endometriosis: 67.4%; Other: 49.0%; Normal pelvis: 52.2%; $p = 0.001$
		Dysuria	Endometriosis: 22.6%; Other: 19.1%; Normal pelvis: 11.0%; $p = 0.03$
		Dyschezia	Endometriosis: 44.2%; Other: 32.7%; Normal pelvis: 25.7%; $p = 0.002$
Heitman 2014[48] Retrospective cohort of consecutive	Histologically verified endometriosis	Premenstrual spotting for ≥2 days	Sensitivity: 76%; Specificity: 90%; PPV: 96%; NPV: 74%; Accuracy: 81%
		Dysmenorrhea	Sensitivity: 87%; Specificity: 63%; PPV: 75%; NPV: 79%; Accuracy: 76%

Table 1. Predictive value of signs, symptoms, and clinical findings for diagnosing endometriosis

Study design and population	Method of diagnosis	Assessment or parameter	Results
women with or without pelvic pain who were evaluated for infertility (N = 80)		Dyspareunia	Sensitivity: 38%; Specificity: 83%; PPV: 74%; NPV: 51%; Accuracy: 58%
Peterson 2013[41]† ENDO Study—Prospective, matched-exposure cohort study comprised of women undergoing pelvic surgery (n = 495) and a matched cohort (n = 131)	Surgically visualized endometriosis (operative cohort) Pelvic MRI-diagnosed endometriosis (matched cohort)	History of infertility Dysmenorrhea Pelvic pain Pelvic pain (surgical indication)	OR, 2.43 (95% CI, 1.57-3.76) [operative]; 7.91 (1.69-37.2) [matched] OR, 2.46 (95% CI, 1.28-4.72) [operative]; 1.41 (0.28-7.14) [matched] OR, 1.39 (95% CI, 0.95-2.04) [operative]; 0.76 (0.09-6.54) [matched] OR, 3.67 (95% CI, 2.44-5.50) [operative]
Nnoaham 2012[43] Prospective,	Laparoscopically visualized endometriosis	Model comprising multiple factors (eg, dysmenorrhea, dyschezia, nonmenstrual pelvic pain, ovarian	Sensitivity: 85%; Specificity: 44%

Table 1. Predictive value of signs, symptoms, and clinical findings for diagnosing endometriosis

Study design and population	Method of diagnosis	Assessment or parameter	Results
observational study of symptomatic women with scheduled laparoscopy (N = 1396)		cyst, family history, race, etc) Model and ultrasound	Sensitivity: 58%; Specificity: 89%
Paulson 2011[54] Prospective cohort of women with chronic pelvic pain (N = 284)	Laparoscopically or histologically confirmed endometriosis	Anterior vaginal wall tenderness (endometriosis and other pathology)	Sensitivity: 93%
		Anterior vaginal wall tenderness (endometriosis only)	Sensitivity: 17%
Droz 2011[65] Retrospective cohort of women evaluated for chronic pelvic pain (N = 331)	Histologically verified endometriosis	Short-form MPQ pain descriptor:	
		Cramping	Sensitivity: 92%; Specificity: 33%; PPV: 40%: NPV: 89%
		Sickening	Sensitivity: 73%; Specificity: 46%; PPV: 40%; NPV: 78%
		Tiring/exhausting	Sensitivity: 77%; Specificity: 38%; PPV: 38%; NPV: 77%
		Shooting	Sensitivity: 70%; Specificity: 43%; PPV: 37%; NPV: 75%
		Punishing/cruel	Sensitivity: 49%; Specificity: 65%; PPV: 40%; NPV: 72%
		Splitting	Sensitivity: 36%; Specificity: 77%; PPV: 43%; NPV: 71%
Paulson 2009[55]	Laparoscopically	Anterior vaginal wall tenderness	Sensitivity: 84%; Specificity: 75%; PPV: 86%; NPV: 69%

Table 1. Predictive value of signs, symptoms, and clinical findings for diagnosing endometriosis

Study design and population	Method of diagnosis	Assessment or parameter	Results
	or histologically confirmed endometriosis		
Prospective study of consecutive women with unexplained infertility (N = 55)			
Meuleman 2009[39]	Histologically verified endometriosis	Pelvic pain	Sensitivity: 59%; Specificity: 56%; PPV: 54%; NPV: 57%
		Pelvic pain and type of infertility, age, and duration of infertility	Sensitivity: 65%; Specificity: 73%
Retrospective case series comprised of infertile women with regular cycles and no prior endometriosis diagnosis (N = 221)			
Hudelist 2009[51]‡	Histologically verified endometriosis	Vaginal exam	Sensitivity: 23-88%; Specificity: 89%-100%; PPV: 65%-100%; NPV: 85%-99%; Accuracy: 86%-99%
		Vaginal exam and TVS	Sensitivity: 67%-100%; Specificity: 86%-100%; PPV: 50%-100%; NPV: 93%-100%; Accuracy: 86%-100%
Prospective study of consecutive women with symptoms of			

Table 1. Predictive value of signs, symptoms, and clinical findings for diagnosing endometriosis

Study design and population	Method of diagnosis	Assessment or parameter	Results
endometriosis (N = 200)			
Flores 2008[44] Respondents to a self-administered questionnaire (N = 1285)	Self-reported surgically confirmed endometriosis	Dysmenorrhea	Cases: 82.5%; General population: 59.3%; $p < 0.001$
		Severe dysmenorrhea	Cases: 65.9%; General population: 52.9%; p = NS
		Dyspareunia	Cases: 52.0%; General population: 20.0%; $p < 0.001$
		Problems conceiving	Cases: 70.6%; General population: 25.2%; $p < 0.001$
		Chronic pelvic pain	Cases: 80.0%; General population: 22.9%; $p < 0.001$
Ballard 2008[45]§ National case-control study comprised of women with endometriosis (n = 5540) and matched controls (n = 21,239)	Diagnostic or procedural codes consistent with endometriosis recorded in a nationwide general practice database	Dysmenorrhea	OR, 9.8 (95% CI, 8.8-10.9)
		Pelvic pain	OR, 13.5 (95% CI, 11.7-15.7)
		Dyspareunia	OR, 9.4 (95% CI, 8.0-11.1)
		Abdominal pain	OR, 5.9 (95% CI, 5.5-6.4)
		Menorrhagia	OR, 5.0 (95% CI, 4.6-5.5)
		Intermenstrual pain	OR, 6.9 (95% CI, 4.7-10.2)
		Infertility/subfertility	OR, 6.2 (95% CI, 5.4-7.1)
		Pelvic inflammatory disease	OR, 6.4 (95% CI, 5.6-7.4)
		Ovarian cysts	OR, 12.2 (95% CI, 9.9-15.0)
		Ovary pain	OR, 9.1 (95% CI, 3.2-26.0)

Table 1. Predictive value of signs, symptoms, and clinical findings for diagnosing endometriosis

Study design and population	Method of diagnosis	Assessment or parameter	Results
Endometriosis (Stages III and IV)			
Peterson 2013[41]†	Surgically visualized endometriosis (operative cohort)	History of infertility	OR, 4.74 (95% CI, 2.57-8.75)
		Dysmenorrhea	OR, 3.43 (95% CI, 1.02-11.5)
ENDO Study—Prospective, matched exposure cohort study comprised of women undergoing pelvic surgery (n = 495)		Pelvic pain	OR, 1.60 (95% CI, 0.89-2.87)
		Pelvic pain (surgical indication)	OR, 4.47 (95% CI, 2.39-8.38)
Nnoaham 2012[43]	Laparoscopically visualized endometriosis	Model comprising multiple factors (eg, dyschezia, ovarian cyst, infertility, cycle length, GI/bladder symptoms, race, etc)	Sensitivity: 71%; Specificity: 85%
Prospective, observational study of symptomatic women with scheduled laparoscopy (N = 1396)		Model with ultrasound	Sensitivity: 82%; Specificity: 76%

Table 1. Predictive value of signs, symptoms, and clinical findings for diagnosing endometriosis

Study design and population	Method of diagnosis	Assessment or parameter	Results
Endometriosis and Other Peri-ovarian Adhesions			
Marasinghe 2014[49] Prospective, observational study comprised of women evaluated for infertility and/or chronic pelvic pain (N = 110)	Laparoscopically visualized endometriosis	Dyspareunia	Sensitivity: 46%; Specificity: 77%; PPV: 52%; NPV: 73%; Accuracy: 47%
		Dysmenorrhea	Sensitivity: 76%; Specificity: 70%; PPV: 57%; NPV: 84%; Accuracy: 71%
		Dyspareunia and dysmenorrhea	Sensitivity: 78%; Specificity: 64%; PPV: 54%; NPV: 85%; Accuracy: 68%
		Vaginal examination	Sensitivity: 73%; Specificity: 88%; PPV: 77%; NPV: 86%; Accuracy: 83%
		Dyspareunia, dysmenorrhea and vaginal exam	Sensitivity: 84%; Specificity: 62%; PPV: 54%; NPV: 88%; Accuracy: 69%
		Fixed ovaries on TVS	Sensitivity: 78%; Specificity: 94%; PPV: 88%; NPV: 89%; Accuracy: 88%
		Dyspareunia, dysmenorrhea, vaginal exam and fixed ovaries	Sensitivity: 92%; Specificity: 61%; PPV: 56%; NPV: 93%; Accuracy: 71%
Deep Endometriosis			
Perello 2017[56]	Histologically verified	Model including previous pregnancy, history of surgery for	Sensitivity: 80%; Specificity: 84%

Table 1. Predictive value of signs, symptoms, and clinical findings for diagnosing endometriosis

Study design and population	Method of diagnosis	Assessment or parameter	Results
Retrospective analysis of consecutive women with ovarian endometrioma who underwent surgery (N = 178)	endometriosis	endometriosis, endometriosis-associated pelvic pain score	
Lafay Pillet 2014[46]¶ Prospective, single-center study of women with a histological diagnosis of endometriosis (N = 211)	Histologically verified endometriosis	Infertility (primary or secondary) Duration of pain >24 months VAS deep dyspareunia >5 VAS GI symptoms ≥5 Severe dysmenorrhea	Sensitivity: 51%; Specificity: 73%; OR, 1.5; $p = 0.003$ Sensitivity: 62%; Specificity: 81%; OR, 7.1; $p < 0.001$ Sensitivity: 69%; Specificity: 59%; OR, 3.2; $p = 0.007$ Sensitivity: 75%; Specificity: 76%; OR, 9.3; $p < 0.001$ Sensitivity: 55%; Specificity: 75%; OR, 3.5; $p < 0.001$
Hudelist 2011[52]‡ Prospective study of	Histologically verified endometriosis	Vaginal exam TVS	Sensitivity: 25%-78%; Specificity: 80%-100%; PPV: 43%-100%; NPV: 84%-98%; Accuracy: 73%-98% Sensitivity: 50%-96%; Specificity: 96%-100%; PPV: 50%-100%;

Table 1. Predictive value of signs, symptoms, and clinical findings for diagnosing endometriosis

Study design and population	Method of diagnosis	Assessment or parameter	Results
premenopausal women with suspected endometriosis (N = 129)			NPV: 90%-99%; Accuracy: 90%-99%
Bazot 2009[53]‡ Retrospective, longitudinal study of consecutive women with clinical evidence of endometriosis (N = 92)	Laparoscopically visualized endometriosis	Vaginal exam	Sensitivity: 18%-74%; Specificity: 72%-96%; PPV: 40%-97%; NPV: 24%-90%; Accuracy: 54%-87%
		TVS	Sensitivity: 9%-94%; Specificity: 67%-100%; PPV: 50%-100%; NPV: 25%-89%; Accuracy: 77%-96%
		Rectal endoscopic sonography	Sensitivity: 7%-89%; Specificity: 44%-100%; PPV: 33%-100%; NPV: 9%-90%; Accuracy: 48%-90%
		MRI	Sensitivity: 55%-87%; Specificity: 86%-99%; PPV: 73%-99%; NPV: 38%-94%; Accuracy: 84%-94%

GI = gastrointestinal; HR = hazard ratio; MPQ = McGill Pain Questionnaire; MRI = magnetic resonance imaging; NPV = negative predictive value; PPV = positive predictive value; TVS = transvaginal sonography; VAS = visual analogue scale.

To identify relevant studies, a search of the MEDLINE database was performed using the following search terms: endometriosis AND (pain OR cycle OR infertility OR “physical exam” OR “physical examination” OR “pelvic exam” OR “pelvic examination”) AND (specificity OR sensitivity OR accuracy). Articles were limited to clinical studies published in English from 2008 through March 2018. Additional studies identified via citations in associated manuscripts were added, if applicable.

*Reported are the agreement between self-reported symptoms of endometriosis and diagnosis of endometriosis recorded in medical records.

Table 1. Predictive value of signs, symptoms, and clinical findings for diagnosing endometriosis

Study design and population	Method of diagnosis	Assessment or parameter	Results

†Data are adjusted odds ratios.

‡Ranges reflect different values based on anatomic locations of the endometriotic lesions.

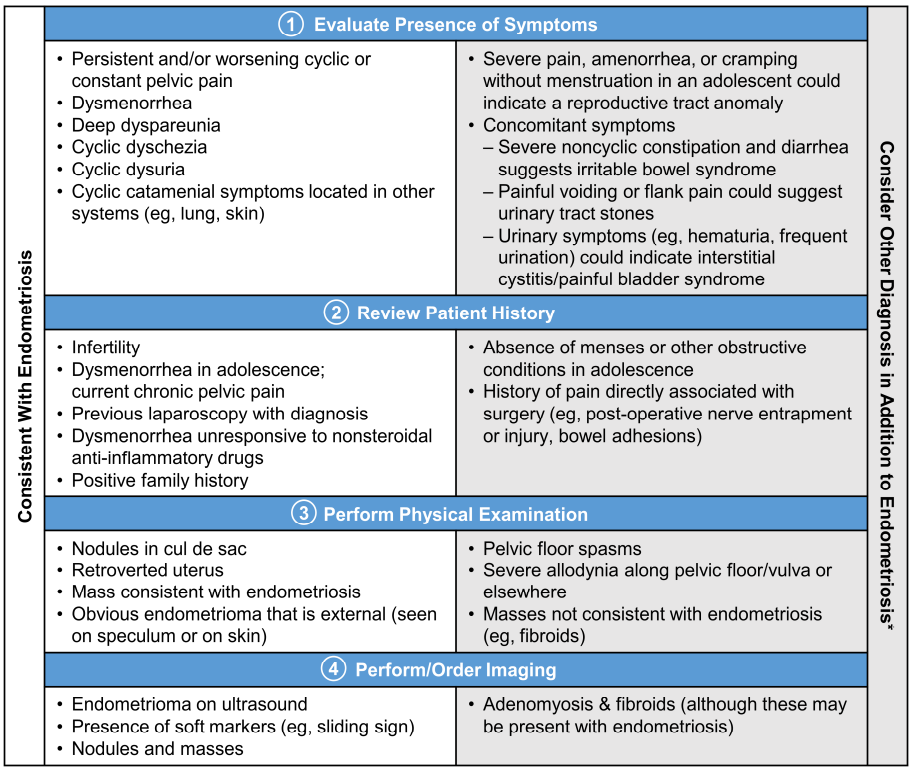
§Shown here are symptoms and signs with an odds ratio for predicting endometriosis of 5.0 or greater.

¶Lafay Pillet et al[18] evaluated combining multiple signs, symptoms, and findings to predict the presence of deep endometriosis. Presented here are the individual measures included in the final model.

Figure Legend

Figure 1. Algorithm for a clinical diagnosis of endometriosis.

Figure 1. Algorithm for a clinical diagnosis of endometriosis



*Alternative diagnoses indicated by symptoms on the right side of the chart may coexist with endometriosis and do not rule out the presence of endometriosis.