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This activity is supported by an educational grant from AbbVie.

**Audience:** This activity was planned for obstetricians and gynecologists and women's health care providers.

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#### Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. Understand the relationship between chronic pelvic pain and endometriosis
2. Understand the limitations of laparoscopy in the diagnosis of endometriosis
3. Understand the emerging role of imaging in the diagnosis of endometriosis

Date of Original Release: April 1, 2019

Date Credits Expire: March 31, 2022

#### Conflict of interest disclosure

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Consultant: Cook Ob/Gyn, Cooper Surgical, IBSA  
GYN Advisory Board: AbbVie, Amag, Therapeutics MD  
Speakers Bureau: Amag, Duchesnay, Therapeutics MD  
Equipment Loan: GE Ultrasound

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Consultant: AbbVie, Bayer, Obseva; received honorarium  
Advisor: Dot Lab; unpaid

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Consultant: AbbVie  
Speakers Bureau: AbbVie, Ferring

#### No disclosures to declare

**Heidi M. Wilson, Course Director**

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April 2019

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# Diagnosing endometriosis: Is laparoscopy the gold standard?

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## Introduction

**E**ndometriosis is a chronic gynecologic condition in which endometrial glands and stroma are found outside of the uterus. It affects approximately 6% to 10% of reproductive-aged women.<sup>1</sup> The most common symptom of endometriosis is pelvic pain that often initially manifests as dysmenorrhea. Typically, the dysmenorrhea is progressive with worsening severity and lengthening duration. In some patients, the pain progresses to chronic and constant pelvic pain, dyspareunia, and/or dyschezia. The pain is classically cyclic, worsening at the time of menses; however, the pain can become continuous, and often debilitating. Even when less severe, pain can limit daily activities and negatively impact a woman's quality of life.<sup>2</sup> Similarly, the pain affects productivity, leading to substantial economic ramifications.<sup>3,4</sup> The other major consequence of endometriosis is infertility; some women may not have pain and are only diagnosed with endometriosis during an infertility investigation. Endometriosis is detected in approximately 50% of women who undergo laparoscopic evaluation during treatment for infertility.<sup>1</sup>

Despite the need for early diagnosis, the multiple presentations and the requirement for surgical diagnosis have often resulted in considerable delays in initiating treatment. The time from symptom presentation until first diagnosis ranges from 7 to 12 years.<sup>3,5,6</sup> Unfortunately many women with endometriosis undergo multiple consultations with specialists who may not have expertise in endometriosis, and as a result are frequently misdiagnosed with gastrointestinal, urologic, or infectious diseases before finally reaching the correct diagnosis.<sup>5</sup>

Laparoscopic visualization generally has been considered the gold standard for diagnosing endometriosis.<sup>1,7-10</sup> However, as will be discussed later in this article, this technique is not without limitations, costs, and risks.<sup>8,9</sup> In practice, physicians often rely on clinical diagnosis as the basis for initiating therapy. This practice recently has been advocated by experts in the field and is consistent with guidance from numerous professional societies.<sup>1,8-11</sup> Most women with chronic pelvic pain that is cyclic in nature, occurring first at the time of menses and that progressively worsens over time, will have endometriosis. Cyclic progressive pelvic pain should be treated as endometriosis in the absence of other easily diagnosed alternatives.

A suspicion of endometriosis may be further supported by family history of the disease or relief of symptoms with prior use of oral contraceptives. In addition, infertility is common among women with endometriosis. Endometriosis should be considered in women with a diagnosis of infertility, especially in those with otherwise unexplained infertility or in those with concomitant pain.

The temporal relationship of pain to the menstrual cycle is informative. Pelvic pain associated with primary dysmenorrhea typically occurs in concert with the onset of menstrual flow and lasts for approximately 8 to 72 hours.<sup>12</sup> Endometriosis pain is progressive, typically cyclic, and can extend beyond the 3-day early follicular phase timeframe associated with primary dysmenorrhea. Primary dysmenorrhea may also be differentiated from secondary dysmen-

orrhea by its rapid response to analgesia with nonsteroidal anti-inflammatory drugs (NSAIDs) as well as the nonprogressive, persistent severity of the pain and continued response to NSAID treatment.<sup>7</sup>

Endometriosis is a chronic disease that deserves early recognition. While laparoscopy will provide a definitive diagnosis, and until reliable biomarkers are available, clinical diagnosis followed by early treatment can provide years of relief and may prevent disease progression.

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## What is the role of laparoscopy?

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The introduction and subsequent widespread application of both diagnostic and operative laparoscopy has led to a revolution in the ability to effectively diagnose and treat gynecologic conditions in a timelier and less invasive manner. Visualization of endometriotic lesions at laparoscopy had become the “gold standard” for the diagnosis of endometriosis. However, it is interesting to note that this description was bestowed in the absence of the performance of rigorous trials. As clinical diagnosis and enhanced imaging studies are beginning to play an important role along with the potential development of circulating or endometrial markers, it is worthwhile to reevaluate the value and accuracy of the diagnosis of endometriosis by laparoscopic visualization.

Several staging systems based on surgical visualization of endometriosis have been introduced.<sup>1,2</sup> However, investigators have demonstrated a lack of correlation between the extent of the disease and symptom severity.<sup>3</sup> There are several possible explanations for this phenomenon. 1) The aforementioned staging systems were designed to assess the potential for pregnancy and not the degree of pain associated with endometriosis. 2) Endometriosis is a pathologic disorder and these scoring systems

are based on visualization of implants and extent of disease without requiring histologic confirmation of the ectopic presence of endometrial glands, stroma, and hemosiderin laden macrophages which defines this disease. 3) It is possible that visualized implants may not always be the sole cause of all associated symptoms, but rather, may reflect a more diffuse inflammatory response within the peritoneal cavity. Of note is the fact that several studies have demonstrated that endometriosis is not always identified in women undergoing surgery for clinically suspected endometriosis or chronic pelvic pain, suggesting either an alternative cause for the pain or a failure of the visualization process.<sup>4,5</sup> 4) Deeply invasive lesions, which can be the cause of severe symptomatology, may not be readily visualized by observation alone, but can require extensive dissection in order to be identified. This task is beyond the scope of a purely diagnostic procedure.

The correlation between laparoscopic visualization of endometriosis with histological confirmation of disease has been evaluated by a variety of investigators who performed laparoscopy for indications of clinically suspected endometriosis, pelvic pain and/or infertility.<sup>6-9</sup> The positive predictive value for laparoscopy in predicting histologically confirmed

**TABLE 1** Diagnosis of endometriosis: Predictive value of visualization at laparoscopy with histologic confirmation

Authors	Year	N	Endometriosis Stage <sup>a</sup>	PPV (%)
Walter et al <sup>7</sup>	2001	44	All	45
Almeida Filho et al <sup>8</sup>	2008	976	All	72
El Bishry et al <sup>9</sup>	2008	48	All	75
			I	33
			III-IV	73-92
Stegmann et al <sup>4</sup>	2008	133	All	64
Fernando et al <sup>5</sup>	2013	431	All	75
			I	50
			III/IV	78-79

Abbreviations: N, number of patients; PPV, positive predictive value.

<sup>a</sup> Revised American Fertility Society Staging<sup>1</sup>

implants ranged considerably from 45% to 87% for all patients. This correlation was particularly weak in patients with stage I endometriosis as compared to those with more extensive stage III and IV disease (TABLE 1, previous page). The subtler and varied appearances of lesions in patients with less advanced disease may have led to a higher degree of variability in diagnostic accuracy among surgeons.<sup>5</sup>

Another variable leading to the high degree of heterogeneity among these studies may be that of implant location. When endometriosis is confirmed by histologic evidence of both endometrial glands and stroma, accuracy is significantly reduced for lesions located on the bladder, pelvic sidewall, and uterosacral ligaments as compared to other locations in the pelvis.<sup>10</sup> Some investigative teams did not routinely describe the site of lesions that were biopsied. One must therefore ask if, given the incidence of nonvisualized deeply invasive endometriosis as well as the presence of microscopic disease, does a failure to simply visualize lesions, particularly in the absence of extensive dissection and biopsy, truly rule out endometriosis?

It is also important to remember that laparoscopy, although a minimally invasive surgery, is still an invasive procedure and is not without risks. Chapron et al reported an overall complication rate associated with laparoscopy to be 9.9% including injury to bladder, bowel, uterus, and vasculature.<sup>11</sup> This does not include the risks associated with anesthesia.

There are, however, still some indications for proceeding directly to surgery (TABLE 2).

In summary, it is important to remember that, although surgical visualization of endometriosis has been considered the gold standard for diagnosis, the approach has highly variable rates of accuracy, particularly in the absence of histologic confirmation of suspected lesions. It would clearly be beneficial to have highly accurate and predictive noninvasive diagnostic markers for endometriosis available, which would better allow the clinician to triage patients to appropriate treatment modalities without having to resort to surgical intervention simply to make a diagnosis. Hopefully, a new and less invasive diagnostic “gold standard” will be at our disposal in the not too distant future.

**TABLE 2** Proposed indications for proceeding directly to laparoscopy in patients with clinically suspected endometriosis

- Suspicious or symptomatic adnexal mass
- Failure to respond to second-line medical therapy
- Desire to conceive in the immediate future after completion of fertility evaluation
- Evidence of deeply invasive disease
- Plan to aggressively excise/ablate all visualized disease as opposed to performing diagnostic procedure only
- Surgical visualization will alter management

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## Role of imaging in diagnosing endometriosis

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Currently, various societies have guideline statements concerning the role of imaging in the diagnosis of endometriosis. The American College of Obstetricians and Gynecologists (ACOG) states that transvaginal ultrasound (TVUS) is the, “preferred imaging technique when assessing endometriosis and/or deep endometriosis of the rectum or rectovaginal septum.”<sup>1</sup> In terms of magnetic resonance imaging (MRI), it should be, “reserved for suspected rectovaginal or bladder endometriosis when ultrasonic tests are equivocal.” In addition, the American Society of Reproductive Medicine (ASRM) differs. It has stated, for both TVUS and MRI, “that imaging modalities have not been found to increase diagnostic accuracy.”<sup>2</sup> Perhaps the Society of Obstetricians and Gynaecologists of Canada (SOGC) stance, in my opinion, is the most reasonable. It states TVUS is, “the first line investigational tool for suspected endometriosis,” whereas MRI, “could be required if deep endometriosis is suspected.”<sup>3</sup>

Hudelist et al reported an increase in the sensitivity for ovarian endometriosis that increased from approximately 30% with pelvic examination alone to greater than 96% with pelvic examination plus TVUS.<sup>4</sup> However, this is utilizing TVUS as an anatomic image, which previously had been the mainstay of how it was being performed. The field has a learning curve just like individuals have a learning curve. Most women’s health care providers would now recognize the ovary, displayed in **FIGURE 1**, as a classic example of an endometrioma. However, we are entering what will hopefully become a new “normal” for the use of TVUS. This is something I would refer to as “dynamic imaging.” Careful examination of the work by Okaro et al underscores this point.<sup>5</sup> They evaluated 120 women who had chronic pelvic pain. What they called “hard markers” (ovarian endometriomas, hydrosalpinges) had a 100% correlation with laparoscopic findings (24 of 24 cases). “Soft markers” defined as reduced ovarian mobility, site-specific



**FIGURE 1** Classic transvaginal ultrasound of an ovarian endometrioma. Now referred to as a “hard marker.”

pelvic tenderness, or the presence of loculated peritoneal fluid were predictive of pelvic pathology in 37 out of 51 women (73%). Many of these women, if examined by a typical anatomic ultrasound survey, would have been classified as “normal.” This underscores the increasing importance of the use of dynamic scanning in patients with chronic pelvic pain. These data further suggest an empiric course of treatment may be appropriate as 61 of 75 women (81%) evaluated by TVUS had such a need for treatment confirmed laparoscopically.

In my opinion, the time has come for all of us who perform TVUS, or those who order TVUS to do, or expect to be done, a dynamic assessment in real time looking for tenderness, decreased mobility and nonanatomically located ovaries (**FIGURE 2**). Realize that normal premenopausal ovaries are typically seen overlying the iliac vessels (**FIGURE 3**). These vessels are retroperitoneal. In lithotomy position, freely mobile ovaries will flop by gravity lateral to the uterus and overlie these vessels. If the patient were placed into a knee-chest position, freely mobile ovaries would move slightly toward the anterior abdominal wall (perhaps 3-5 cm). When adhesions exist, ovaries may well appear anatomically normal in size and appearance but not necessarily in location. While not diagnostic of



**FIGURE 2** An example of a normal ovary stuck behind and to the uterus. Lack of mobility and pain only appreciated with dynamic scanning. Such “soft markers” have a very high sensitivity for pelvic pathology (73%).



**FIGURE 3** A normal ovary in the proliferative phase seen overlying the iliac vessels (which remember are retroperitoneal). This finding virtually excludes any extensive adhesive disease.

adhesions, when coupled with pain on movement with a vaginal probe, or a lack of mobility of such ovaries, one’s index suspicion for pathology should be greatly increased.

### How do we improve on earlier and non-laparoscopic diagnosis of endometriosis?

The first step is education, especially of non-women’s health care providers. They need to be made to understand that, in women with pelvic pain, referral to qualified women’s health care providers much earlier in the course is indicated. Better education of women’s health care providers is essential as well. When first-line therapies for chronic pelvic pain such as analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and oral contraceptives are not sufficiently effective, the clinician should entertain a diagnosis of possible endometriosis. Secondly, a shift in how we think about and use TVUS is essential. Certainly, an anatomic “hard marker,” like a classic endometrioma, makes a definitive diagnosis. However, as already stated, dynamic TVUS should become the standard practice for the person performing the exam and the routine expectation of the person ordering the exam. “Soft markers,” already discussed, in patients with chronic pelvic pain will have a very high positive predictive value but only if such techniques are routinely thought about and employed. While there are few data to objectively validate that

early accurate diagnosis and treatment improve long-term outcomes, clinical experience and expert opinions support the possibility that early diagnosis will reduce long-term morbidity.<sup>6</sup>

In summary, while in the past many clinicians believed that therapies targeting endometriosis needed a confirmatory laparoscopy, increasingly a clinical and/or sonographic diagnosis can be adequately suspected as discussed in this article to begin pharmacotherapy without first resulting to diagnostic laparoscopy.

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