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State-of-the-Art Review

Strengths and limitations of diagnostic tools for endometriosis and relevance in diagnostic test accuracy research

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ABSTRACT

Endometriosis is a chronic systemic disease that can cause pain, infertility and reduced quality of life. Diagnosing endometriosis remains challenging, which yields diagnostic delays for patients. Research on diagnostic test accuracy in endometriosis can be difficult due to verification bias, as not all patients with endometriosis undergo definitive diagnostic testing. The purpose of this State-of-the-Art Review is to provide a comprehensive update on the strengths and limitations of the diagnostic modalities used in endometriosis and discuss the relevance of diagnostic test accuracy research pertaining to each. We performed a comprehensive literature review of the following methods: clinical assessment including history and physical examination, biomarkers, diagnostic imaging, surgical diagnosis and histopathology. Our review suggests that, although non-invasive diagnostic methods, such as clinical assessment, ultrasound and magnetic resonance imaging, do not yet qualify formally as replacement tests for surgery in diagnosing all subtypes of endometriosis, they are likely to be appropriate for advanced stages of endometriosis. We also demonstrate in our review that all methods have strengths and limitations, leading to our conclusion that there should not be a single gold-standard diagnostic method for endometriosis, but rather, multiple accepted diagnostic methods appropriate for different circumstances. © 2022 International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

Objectives

The process of diagnosing endometriosis is controversial and a dynamic area of research. The purpose of this State-of-the-Art Review is to consider the strengths and limitations of the various proposed methods to diagnose endometriosis, including clinical history and physical examination, imaging, surgery and histopathology. We aim to discuss the strengths and limitations of these diagnostic methods and their roles in diagnostic test accuracy (DTA) research in endometriosis. Biomarkers as a diagnostic tool are reviewed in Appendix S1. We set the stage by describing endometriosis and its subtypes. We then review basic DTA principles and delve into how these principles are applied to endometriosis in clinical practice and research settings.

Endometriosis is a benign disease and, unlike malignant tumors, diagnostic confirmation is not performed in all patients as treatment is only required if there are demonstrable negative effects on an individuals' quality of life (QoL). In those without symptoms or signs, such as infertility, there would be no indication to perform diagnostic testing for endometriosis. The clinical decision to perform surgery varies not only with the estimated probability of diagnosis, but also the impact of symptoms on QoL, estimated extent/location of disease, risk of complications and experience of the surgeon. Thus, the accuracy of a diagnostic test is confounded by the fact that histological

confirmation is not sought universally. This review aims to help readers understand the limitations of diagnostic methods and complexity of clinical decision-making in people with signs and symptoms of endometriosis.

What is endometriosis?

Endometriosis is a chronic inflammatory condition that affects up to 10% of people assigned female at birth[1,2]. While endometriosis affects primarily cis-gendered women, we recognize that there are people living with endometriosis who are transgender, do not menstruate, do not have a uterus or do not identify with the terms used in the literature; henceforth, we refer to this population using gender-neutral terms unless we are referencing specific studies that included exclusively women. The condition is defined by the presence of endometrial-like tissue outside of the uterine cavity[3], most commonly associated with dysmenorrhea, chronic pelvic pain (CPP) and infertility[4]. Although many people with pelvic pain and infertility are diagnosed with endometriosis at the time of surgery, up to 50% of those with evidence of endometriosis at the time of laparoscopy have no symptoms at all[5], highlighting the enigmatic nature of this condition.

The symptoms of endometriosis can be cyclical or chronic, are often non-specific and can mimic those caused by other gynecological, gastrointestinal and musculoskeletal disorders[6]. Given the heterogeneity of presenting symptoms, the diagnostic journey for many people with endometriosis is long and arduous. The delay between symptom onset and diagnosis is well documented, with 4–12-year delays reported in the literature[7–9]. Menstrual symptoms may be normalized by health professionals and patients alike, contributing to diagnostic delay and prohibiting treatment[8,9]. Symptomatic people with untreated endometriosis may experience significant reduction in QoL, as symptoms contribute to decreased physical and psychological performance, poor sleep quality, impaired sexual function and perceived stress[10,11]. It has been suggested that endometriosis is a progressive disease and that early diagnosis and treatment have the potential to reduce disease progression, adhesion formation, associated infertility and central pain sensitization precipitating CPP[12]. Qualitative data suggest that people benefit from a diagnosis as it validates their symptoms, provides a language in which to discuss their condition, gives reassurance that symptoms are not secondary to a malignant process and offers possible management strategies[7,13].

Subtypes of endometriosis

Endometriosis is often categorized into three subtypes: superficial endometriosis (SE), ovarian endometriosis (OE) (also known as endometriomas) and deep endometriosis (DE)[14]. Uterine adenomyosis is characterized by the presence of endometrial-like glands and stroma within the myometrium and its subtypes include intrinsic adenomyosis, extrinsic adenomyosis, adenomyosis externa and focal adenomyosis of the outer myometrium (FAOM). It has been proposed that adenomyosis and endometriosis represent different phenotypes of a single disease, with extrinsic adenomyosis resulting from pelvic endometriosis and FAOM from rectal/bladder DE[15]. In this review, we focus on diagnostic testing for conditions considered traditionally as endometriosis, i.e. SE, OE and DE.

Importantly, DE lacks a consistent definition. A landmark study by Martin *et al.* demonstrated that endometriotic lesions penetrated > 5 mm in 25% of examined women and these were classified as 'deep' lesions[16]. A subsequent study examining pathological characteristics of lesions with various depths suggested that lesions penetrating > 5 mm demonstrate pathological features of invasive or active disease[17]. Alternatively, DE has been defined as a fibrous/muscular infiltration of organs and anatomical structures containing endometrial-like tissue below the peritoneum, regardless of the depth of infiltration[18]. An international working group of the American Association of Gynecologic Laparoscopists (AAGL), European Society for Gynaecological Endoscopy (ESGE), European Society of Human Reproduction and Embryology (ESHRE) and World Endometriosis Society (WES) published recently an updated terminology for endometriosis and elected to remove the requirement to measure a lesion to differentiate SE from DE based on the challenges in measuring lesions surgically[19]. The opinion-based consensus was to define DE as 'endometrium-like tissue lesions in the abdomen, extending on or under the peritoneal surface [that] are usually nodular, able to invade adjacent structures, and associated with fibrosis and disruption of normal anatomy'. In the DTA literature, DE is most commonly considered to be endometrial-like tissue with a depth > 5 mm[20], however, the definition of DE and its relation to SE has a significant bearing on DTA research as discussed below.

Diagnosing endometriosis: presence or absence

Laparoscopy is considered to be the current gold standard for diagnosing endometriosis[3,21,22]. Laparoscopy permits two diagnostic techniques: direct visualization of endometriosis and histological assessment via biopsy. Often, these are combined because biopsy is usually reliant on a visual diagnosis[23].

Surgical and histological diagnosis of endometriosis was a requisite historically for people presenting with symptoms of pelvic pain and infertility to access treatment[24]. As such, the delay in medical or surgical treatment of endometriosis is likely, in part, secondary to the perceived need to use surgery as a diagnostic tool. To overcome the negative outcomes of waiting for a surgical diagnosis, there has been a paradigm shift to prescribe empirical medical therapy before or instead of laparoscopy to people presenting with symptoms of endometriosis, unless fertility is a priority[25]. This has unveiled a diagnostic category often called clinical diagnosis[26], which tends to combine the clinical history and physical examination. While it may be advantageous for individuals' symptoms

to be acknowledged and attributed potentially to endometriosis, offering the possibility of early treatment, clinical diagnosis carries controversy because of poor diagnostic performance and the diagnostic uncertainty that ensues amongst patients and healthcare providers[27,28]. Imaging techniques, including transvaginal ultrasound (TVS), transrectal ultrasound (TRS) and magnetic resonance imaging (MRI), can bridge the gap between clinical and surgical diagnosis by providing a visual diagnosis that is non-invasive and can be achieved more quickly, safely and accessibly compared with surgery. As with clinical and surgical diagnostic methods, controversy and challenges exist with imaging-based diagnosis that will be discussed in detail below.

Diagnosing endometriosis: extent of disease

Diagnosing endometriosis is much more than stating its presence or absence; the subtype, location and extent of disease are important considerations in clinical management. In addition, endometriosis can manifest in non-gynecological organs including the gastrointestinal tract and, less commonly, the urinary tract, diaphragm and thorax[29]. When surgical management is considered, advanced laparoscopic skills are often needed. Preoperative understanding of disease extent may prevent unpredictable, incomplete or abandoned surgical attempts and suboptimal resection of endometriosis[30]. Residual disease can lead to persistent pain and a higher complication rate in case of reoperation[31]. Awareness of disease extent preoperatively may allow surgeons to predict the complexity of the operation and consider the need for involvement of a multidisciplinary team, and to better estimate surgical risks[32]. Figure 1 demonstrates the various appearances of a case of parametrial DE on physical examination, TVS and laparoscopy. One can appreciate the significant heterogeneity in lesion appearance and how a preoperative understanding of symptoms[33] and lesion extent may alter surgical counseling and treatment options. For these reasons, it is imperative to utilize diagnostic tools that can diagnose endometriosis subtypes, location and disease extent accurately to guide appropriate treatment.

Assessing diagnostic test accuracy

The utility and validity of a diagnostic test are defined mainly by its sensitivity and specificity for a particular condition. However, these metrics can sometimes be difficult to interpret and translate into clinical decision-making. The clinician needs to know the probability that a positive or negative test predicts correctly that an individual does (positive predictive value (PPV)) or does not (negative predictive value (NPV)) have the disease[34]. As prevalence increases so does PPV and as prevalence decreases the NPV increases[34]. A test performed at a tertiary endometriosis referral center with a much higher prevalence of disease would be presumed to have a higher PPV as compared with a test performed in a community center with lower disease prevalence, despite equivalent sensitivities and specificities. Thus, the reported PPV and NPV of a diagnostic test are biased, and inappropriate clinical decisions may be made if diagnostic tests are not adjusted to account for local prevalence[35]. The likelihood ratio (LR) is the likelihood that a given test result would be expected in a patient with the target disorder compared with the likelihood that the same result would be expected in a patient without the target disorder. LR is used to assess the utility of a diagnostic test and to select appropriate testing modalities for a certain disease, particularly as it is less likely to change with disease prevalence.

When considering a novel diagnostic modality, its sensitivity and specificity should be compared with those of current gold-standard methods. In the case of endometriosis, direct visualization and histopathology have been traditionally considered the gold standard against which all other diagnostic tests are compared. According to the 2015 STARD (Standards for Reporting Diagnostic Accuracy Studies) guidelines, the index test and reference standards should be explained in sufficient detail to allow replication, as differences in test performance may be a source of variation in diagnostic accuracy[36]. In endometriosis DTA research, it is important to highlight the skill levels of those undertaking the index and reference tests (i.e. sonography, image interpretation, surgery), as test accuracy relies on their level of expertise.

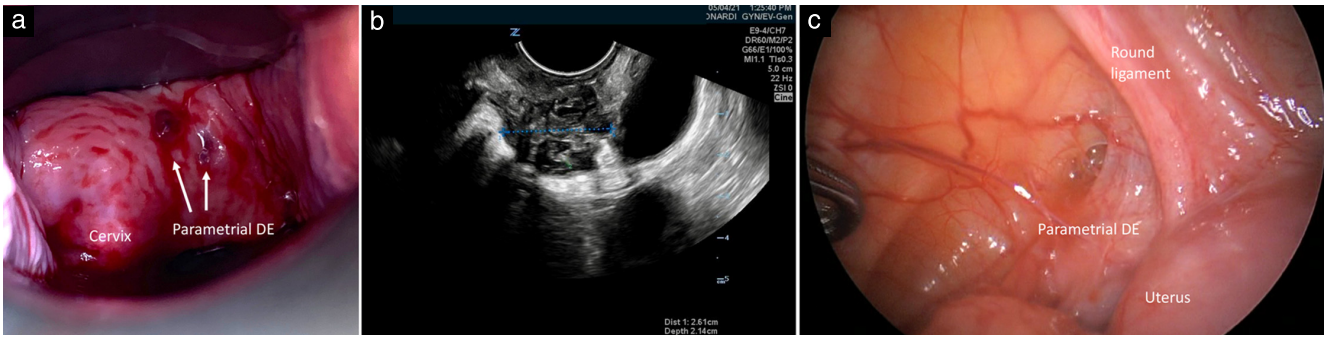

Figure 1 Visualization of parametrial deep endometriosis (DE) in same patient on speculum examination (a), transvaginal ultrasound (b) and laparoscopy (c). (a) On speculum examination, the most caudal aspect of the lesion is visualized anterior to the cervix. This visualized aspect represents only a small part of the underlying lesion, as seen on transvaginal ultrasound (b). (c) On laparoscopy, the irregularity of the peritoneum can be appreciated, although the full extent of the parametrial lesion cannot be discerned.

In addition, the different purposes of diagnostic tests should be considered[37]. Firstly, a test may be used as a new instrument of diagnosis, meaning that it has an equivalent or higher accuracy of diagnosis compared with the current gold standard, potentially along with other advantages. This would be considered a replacement test. Secondly, a test may be used to triage people for further and potentially more invasive testing. A highly specific triage test can rule in endometriosis, and people with a positive test can proceed confidently with treatment depending on their symptoms and goals. Lastly, an adjunct test can be used in addition to an existing test to improve diagnostic accuracy.

An additional challenge in endometriosis DTA research is verification bias, since not all people with the disease undergo laparoscopy and therefore the true disease state is unknown in a subset of patients[38]. As people with endometriosis may undergo multiple diagnostic tests prior to surgical/histological diagnosis, the combined accuracy of tests with verification bias must be considered. Recently, sequential testing has been evaluated using conditional Bayesian analysis. Bayesian inference reflects clinical practice, as clinical symptoms and physical examination are considered first, to inform which tests will be performed[39].

We proceed to discuss the strengths and limitations of each of the current and potential diagnostic methods for endometriosis and their role in DTA research.

DIAGNOSTIC METHODS

Clinical diagnosis

A clinical diagnosis of endometriosis is based upon the individual's clinical signs and symptoms and physical examination. An increase in the utilization of clinical diagnosis has been advocated by a group of endometriosis experts[26]. A detailed clinical history should be taken with particular emphasis on the most common symptoms and signs of endometriosis and their severity, including gynecological symptoms, such as dysmenorrhea, cyclical and non-cyclical pelvic pain, deep dyspareunia and infertility, and non-gynecological cyclical symptoms, such as dyschezia, dysuria, hematuria, flank pain, rectal bleeding and shoulder pain[40]. The visual analog scale (VAS) has been found to represent the best-adapted tool for measuring pain in endometriosis[41] and is generally employed in studies assessing DTA of clinical assessment.

Physical examination in people with suspected endometriosis should include examination of the pelvis and inspection and palpation of the abdomen[40]. The pelvic examination should include a speculum examination to define the presence or absence of posterior vaginal fornix (PVF) endometriosis, which may be visualized if present. A digital vaginal examination should be performed to define the presence or absence of nodules within the uterosacral ligaments (USLs), torus uterinus, PVF, rectovaginal septum (RVS), low rectum and parametrium. This should include a bimanual examination to assess uterine size, orientation and mobility/fixation, presence of adnexal masses and site-specific tenderness in the pelvis, including through the pelvic floor musculature[42].

Traditionally, the central tenet of endometriosis diagnosis has focused on the identification of endometriotic lesions in the pelvis during surgical inspection. Initially employing clinical diagnostic methodologies shifts the focus of diagnosis from the lesions to the patient[26]. This shift reinforces the role of empirical medical treatment, albeit potentially to the detriment of legitimization and social support based on a more tangible visible diagnosis, and limits the uncertain effect of surgery on disease/symptom progression. Clinical diagnosis was demonstrated to decrease diagnostic delay by Soliman *et al.* wherein the mean time from initial consultation to diagnosis was shortened when non-surgical methods were used as compared with surgical diagnosis[43]. As diagnosis is often the gatekeeper to treatment, an expeditious diagnosis may lead to patients receiving confirmation of endometriosis earlier and starting treatment sooner.

Clinical history

Strengths. In a comparative study of 90 women scheduled to undergo laparoscopy for possible endometriosis, the diagnostic accuracy of common clinical symptoms of endometriosis (dysmenorrhea, pelvic pain, dyspareunia and infertility) was assessed. Any of these four symptoms present on clinical history predicted a diagnosis of endometriosis with a sensitivity of 76% and specificity of 58%, as confirmed by laparoscopy and histopathology[44]. A more recent study evaluated the DTA of certain clinical symptoms in 148 women aged < 55 years with CPP (> 6 months)[45]. This study found that a combination of infertility and pain that increases during menses predicted endometriosis (as verified by laparoscopy) with a specificity of 98%, although the sensitivity of this combination of symptoms was only 20%. Irregular menses and pain that increases during menses were found to predict a diagnosis of endometriosis with 76% sensitivity and 51% specificity[45]. A larger retrospective analysis of 5500 British women aged 15–55 diagnosed with endometriosis on chart review described symptoms that are predictive of diagnosis of endometriosis, as compared with age-matched controls. Predictive symptoms included severe dysmenorrhea in infertile women, abdominopelvic pain, heavy menstrual bleeding, dyspareunia, postcoital bleeding and/or previous diagnosis of ovarian cyst, irritable bowel syndrome and pelvic inflammatory disease[46]. It was demonstrated that the likelihood of endometriosis increases with the number of symptoms present, from an odds ratio of 5.0 with one symptom present to 84.7 with seven or more symptoms present[46]. Other information including absenteeism from school/work due to dysmenorrhea and a family history of endometriosis have been demonstrated to be associated strongly with disease presence. In addition to the diagnostic predictive value of the clinical assessment, there may be additional therapeutic benefits to obtaining a detailed history in

people affected by chronic pain. The clinical interview offers an opportunity for people to share their experiences and may contribute to the development of a therapeutic alliance between patient and provider.

Features of a patient's clinical history and symptom description may assist clinicians in identifying disease location. The ENZIAN score has been developed to grade endometriosis lesion extent and location[33]. A retrospective study by Montanari *et al.* demonstrated that disease location and extent as described by the revised ENZIAN score was correlated with the presence and severity of preoperative symptoms[33]. Specifically, dyspareunia was associated with disease in ENZIAN compartment B (USL and parametrium), dyschezia was associated with disease in ENZIAN compartment C (rectum, sigmoid colon) and dysuria was associated with disease in ENZIAN compartment FB (bladder).

Limitations. While clinical history is generally indicated in an initial assessment, there are limitations to its accuracy in predicting a diagnosis of endometriosis. Firstly, how a person perceives and communicates their symptoms may be highly variable and subjective. Extrapolating from the chronic back pain literature, the emotional experiences associated with chronic pain are variable and can trigger differing behavioral responses ranging from avoidance to functional or adaptive behaviors[47]. This variability in pain experience may influence a clinician's perception of their patient's pain symptoms and adds subjectivity to the clinical assessment on the clinician's end, confounding diagnostic accuracy.

In addition, common symptoms associated with endometriosis such as pain and infertility can have multiple gynecological and non-gynecological causes. A review of CPP pathogenesis discusses frequent non-endometriotic causes of CPP which include pelvic adhesions, pelvic venous congestion, interstitial cystitis, myofascial pain and irritable bowel syndrome[6]. Psychosocial factors such as a history of sexual trauma may predispose some to somatization and CPP[48]. Among subjects with a diagnosis of endometriosis at the time of laparoscopy, pain scores have generally been reported to be higher as compared to those of subjects with other etiologies for pain or a normal-appearing pelvis[49].

It is unclear whether symptom presence or severity can differentiate endometriotic disease subtype or predict the extent of disease. Chapron *et al.* assessed the ability of a standardized preoperative questionnaire to predict posterior-compartment DE[50]. The analysis demonstrated that overall dysmenorrhea and dyspareunia scores, as assessed by VAS, were equivalent in women presenting with DE and other types of endometriosis (SE and OE). Variables found to be independent predictors for posterior DE included cyclical dyschezia, severe dyspareunia and previous surgery for endometriosis. The overall sensitivity and specificity of this questionnaire for diagnosing posterior-compartment DE was 74.5% and 68.7%, respectively[50], indicating lower diagnostic performance compared with laparoscopy[51].

In a multivariate analysis of over 1000 women with endometriosis undergoing surgery, performed by Vercellini *et al.*, it was demonstrated that no correlation exists between the severity of pain and the extent of disease as characterized by the most recently revised American Society for Reproductive Medicine (rASRM) endometriosis staging system[52]. The generally accepted notion has been that disease extent in the pelvis (as graded by visualization at the time of laparoscopy) does not correlate with symptom severity. However, rASRM was developed for infertility purposes and does not include staging of DE, nor has it been validated to predict fertility and pain outcomes before and after surgery.

Physical examination

Strengths. The physical examination offers a non-invasive opportunity to detect endometriosis by visualization or palpation and to assess sites of pain and organ mobility. Certainly, visualization and palpation of endometriosis within the vagina (Figure 2) raises clinical suspicion that more extensive disease is present and can guide further assessment. From a resource perspective, physical examination performed by an adequately trained clinician is financially accessible and timely as it does not depend on the availability of imaging modalities or surgical facilities.

Comparative data have demonstrated that physical examination can predict a diagnosis of endometriosis with high accuracy, depending on its anatomic location[44,53,54]. In a study by Hudelist *et al.* of 200 women with symptoms suggestive of endometriosis, a physical exam was considered positive if there was palpable nodularity, thickened or stiffened tissue, or a palpable cyst within the vagina,

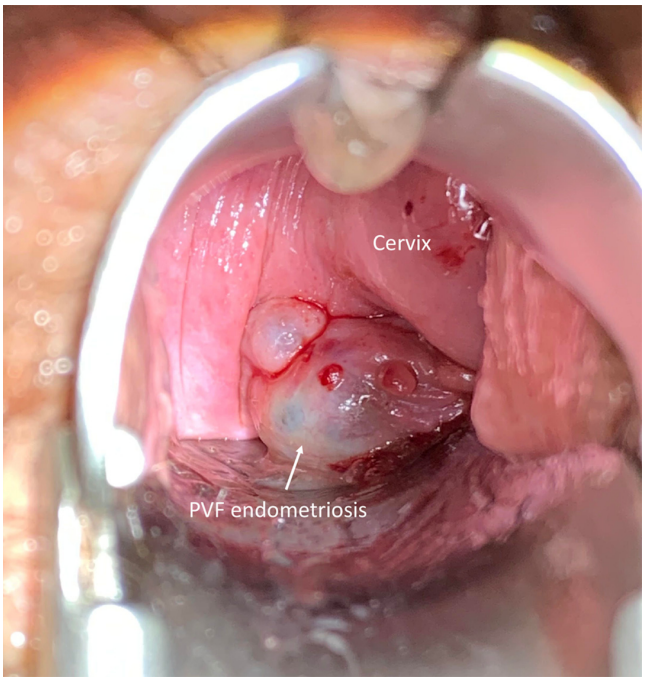

Figure 2 Endometriosis visualized in the posterior vaginal fornix (PVF) on speculum examination. This finding strongly suggests the presence of more extensive disease.

USLs, RVS, pouch of Douglas (POD), rectosigmoid or posterior wall of the urinary bladder[53]. A positive examination had a specificity of 89–100% for endometriosis in these various locations on laparoscopy. The sensitivity of physical examination was relatively high for detection of endometriosis in the RVS (88%) and POD (70%), although it fared poorer in detecting endometriosis in the ovaries and bladder, with sensitivities as low as 23% and 25%, respectively[53]. A similar comparative study by Bazot *et al.* found that the physical examination had relatively high specificity, ranging from 72–96%[54]. The sensitivity was highest for the detection of USL endometriosis, at 73%, and lower for detection of RVS, intestinal and vaginal endometriosis, at 18%, 46% and 50%, respectively[54]. Notably, all examinations were performed by physicians specializing in endometriosis and the prevalence of DE was high in this sample. Given the low-risk nature and relatively high specificity of the physical exam, it is well suited as a first-line test for people presenting with a clinical history suggestive of endometriosis.

Limitations. Laparoscopically proven endometriosis has been diagnosed in more than 50% of women with a clinically normal pelvic examination[44]. We believe that the outcomes of a physical examination for detection of endometriosis are dependent on the experience of the examining clinician. Moreover, physical examination may not be tolerated by many people with suspected endometriosis due to pelvic pain and bimanual examination may not be reasonable or feasible in adolescents, non-sexually active individuals or those affected by previous sexual trauma.

Results of routine clinical examination vary significantly with the location of DE, with one study reporting that 80% of vaginal lesions were detected on clinical exam as compared to 35% of DE in the rectum and 33% of DE in the USLs[55]. As no studies, to our knowledge, have assessed the diagnostic accuracy of physical examination in detecting SE, this diagnostic modality can only be analyzed in the context of detecting DE and cannot be relied on to differentiate subtypes of disease, limiting its clinical applicability. In addition, the dynamic assessment of organ mobility (e.g. ovarian mobility) is difficult by physical examination. Although it is possible to appreciate limited uterine mobility and nodularity within the POD, the sensitivity for prediction of POD obliteration is very poor, especially compared to the TVS uterine sliding sign[56].

Relevance in DTA studies. In their review of clinical diagnostic methods, Agarwal *et al.* compiled data on the accuracy of clinical assessments for diagnosing endometriosis and noted that the studies were highly heterogeneous, precluding meaningful meta-analysis of the data[26]. Studies that aim to diagnose endometriosis by clinical assessment require surgical and histological confirmation, yielding verification bias, as the true diagnosis in those who do not undergo surgery cannot be determined. The decision to perform surgery is subject to multiple forms of bias, leaving the results of DTA studies confounded by uncontrollable factors. Studies on clinical assessment DTA are often retrospective and subject to recall bias or incomplete data. Many retrospective DTA studies on clinical assessment rely on a diagnosis of endometriosis written in the patient's chart to confirm diagnosis, creating ambiguity as to whether the disease was histologically confirmed. Performing prospective studies would be valuable but would need to account for factors such as recruitment site and duration and evolution of symptoms.

Most studies on DTA for endometriosis take place in tertiary academic centers, which are not always the first point of contact for a person at the time of symptom onset/recognition. Findings of DTA studies on clinical assessment may not be generalizable for clinicians assessing someone for the first time with symptoms of endometriosis, which may also be related to a myriad of conditions, both gynecological and non-gynecological in origin. Presumably, the experience and skill in the clinical examination will not be as strong amongst primary care providers and generalist obstetrician–gynecologists as those in tertiary centers with endometriosis-focused practices. In addition, it is important to consider the overall low prevalence of detectable DE on physical examination. PVF DE is a less frequent form of disease and is the only type of pelvic endometriosis that can be visualized directly on physical examination. The PPV and NPV of the physical examination may be impacted by low prevalence and this should be considered when interpreting DTA data.

Diagnostic imaging

Diagnostic imaging encompasses ultrasound, MRI, computed tomography, nuclear medicine and X-ray. Here, we focus on ultrasound and MRI only, as these are the most frequently employed diagnostic imaging modalities in endometriosis at present (although others are being considered and studied)[57]. Depending on the local regulation and organization of medical practice, the performance and image interpretation stages may be carried out by different individuals, particularly for ultrasound. In general, there are two systems: the first is a combination of sonographer and radiologist, whereby the sonographer performs the ultrasound assessment, capturing images and videos that are interpreted by an imaging expert (i.e. radiologist, gynecologist with subspecialty training). The second model involves a sonologist who is usually a gynecologist with specialized obstetrics/gynecology-focused ultrasound training and optimal knowledge of endometriosis. This model functions commonly in tertiary centers and specialized clinics. It may or may not involve a sonographer performing the ultrasound assessment and when it does not, the sonologist performs and interprets the ultrasound simultaneously at the point of care (i.e. within the clinical consultation).

Ultrasound

Historically, OE was thought to be the only subtype of endometriosis diagnosable with ultrasound. Ultrasound is becoming increasingly and inextricably linked to

the modern practice of gynecological surgery. The gynecological surgeon sonologist[58] has clinical expertise in the performance and interpretation of gynecological ultrasound, and uses ultrasound as an extension of the physical exam in the diagnosis and management of endometriosis. Radiologists, too, have expanded their knowledge of endometriosis ultrasound and some are adopting the technique more routinely[59,60]. Despite these advancements, the American Institute for Ultrasound in Medicine (AIUM) simply recommends that pelvic ultrasound include assessment of the uterus, ovaries and rectouterine pouch for fluid or 'mass' by transabdominal ultrasound and/or TVS[61]. On the other hand, the International Deep Endometriosis Analysis (IDEA) group recommends a more thorough ultrasound assessment beyond the basic steps to identify DE and adhesions caused by endometriosis[42]. This includes an assessment of anatomic structures in the anterior compartment (bladder, ureter) and posterior compartment (bowel, USLs, RVS, PVF and POD) for DE and assessment of pelvic organ mobility[62]. Contrast-enhanced TVS, defined as methods using free fluid, saline, water or gel in the rectum, vagina or POD, or excess gel in the ultrasound probe cover to create an acoustic window or a stand-off view, could be add-on options for TVS.

For some people, TVS may not be feasible and TRS could be considered, as per the IDEA consensus. TRS has demonstrated good diagnostic accuracy for bowel, RVS and PVF endometriosis, but may be considered a second-line approach due to its perceived invasiveness and potentially negative experience[63].

Novel imaging modalities beyond traditional TVS or TRS also exist, such as three-dimensional (3D) techniques and artificial intelligence (AI) methods. The utility of these newer approaches for DE assessment has yet to be proven. 3D-TVS techniques enable the acquisition of ultrasonographic volumetric data with a single sweep of the ultrasound beam, which can be used in real time or later viewed and compared. However, 3D-TVS is dependent on the quality of the 2D image obtained and may perform better in real time. AI methods involve the use of complex algorithms which facilitate machine learning, and AI has been proposed in the field of gynecological ultrasound for evaluation of the uterus[64], ovarian cysts[65], DE[66] and POD obliteration[67]. While the diagnostic accuracy of 3D-TVS and AI in endometriosis has been studied[66,68,69], these methods are currently limited by a lack of external validation and comparative superiority to 2D-TVS.

Strengths. Ultrasound is a dynamic test allowing real-time assessment. From a DTA perspective, TVS has been demonstrated to be superior to physical examination in comparative studies, specifically in diagnosing OE and posterior-compartment endometriosis[27,28,70]. In a Cochrane review, Nisenblat *et al.* summarized all published studies evaluating the accuracy of TVS in diagnosing endometriosis[71]. The review included five studies (1222 women) evaluating the diagnosis of pelvic endometriosis, eight studies (765 women) assessing the diagnosis of OE and nine studies (934 women) evaluating the diagnosis of DE. For each imaging test, data were classified as positive or negative for surgical detection of endometriosis. The review concluded that people with evidence of endometriosis identified on TVS were likely to have endometriosis (diagnostic test performance approached the criteria of a triage test to rule in endometriosis), eliminating the need to perform laparoscopic surgery for *diagnostic* purposes in these people. TVS was found to be sufficiently accurate to determine whether OE was present and surgical excision was needed, with reported sensitivity and specificity of 93% and 96% respectively[71]. This finding is corroborated by an earlier systematic review that concluded that TVS has clinical utility in differentiating OE from other types of ovarian cysts or masses[72].

Nisenblat *et al.* evaluated the DTA of TVS for DE and reported a sensitivity of 79% (95% CI, 69–89%) and specificity of 94% (95% CI, 88–100%)[71]. Mapping of DE to specific anatomic sites within the pelvis was also reviewed. TVS was found to detect USL endometriosis with a sensitivity of 64% (95% CI, 50–79%) and specificity of 97% (95% CI, 93–100%). The utility of TVS in identifying DE has been well documented[71,73–76]. Specifically, a recent systematic review and meta-analysis on the accuracy of TVS for diagnosis of DE in the USLs, RVS and vagina demonstrated similar diagnostic performance with overall lower sensitivity and high specificity for DE detection in each of these locations[76].

The dynamic TVS test, the uterine sliding sign, is highly accurate at discerning POD obliteration, with sensitivity and specificity of 83–100% and 91–100%, respectively[77–79]. The uterine sliding sign involves applying gentle pressure to the cervix to mobilize the uterus in order to determine whether the anterior rectum glides freely over the posterior vagina, cervix and uterus[77]. Lack of sliding is a 'soft marker' for the presence of rectal endometriosis[80]. There is high inter- and intraobserver agreement for predicting POD obliteration amongst gynecological sonologists[81]. Interpretation of this sign involves a steep learning curve and requires a minimum degree of training[82], although the number of practice scans required to be considered competent may vary by trainee[83]. Ovarian immobility at the time of TVS is another important soft marker that has been associated with OE[84,85], posterior-compartment DE[86] and ipsilateral SE[87–89], as ipsilateral pelvic sidewall SE is less likely to be present in people with a mobile ovary (in the absence of DE or OE)[89]. Ovarian immobility to the pelvic sidewall is important to identify, using preoperative TVS, for patient counseling and surgical planning, as these women are at increased risk of requiring pelvic sidewall adhesiolysis and ureterolysis[90].

Endometriosis of the rectosigmoid, colon or bladder can be subtyped into SE or DE. Bladder and bowel DE are defined as the presence of endometriotic tissue invading the detrusor muscle[91] and the muscularis propria of the bowel[92], respectively. A meta-analysis by Gerges *et al.* of 30 studies evaluated the diagnostic accuracy of TVS for the non-invasive preoperative detection of DE in

the rectosigmoid[93]. Pooled sensitivities and specificities were high at 89% and 97%, respectively[93]. Another three systematic reviews and meta-analyses demonstrated comparable sensitivities and specificities of TVS for bowel DE[71,75,94]. TVS has also been demonstrated to assess accurately rectosigmoid DE lesion size[95] and lesion-to-anal verge distance[96]. These factors can be helpful in preoperative planning, for example when deciding surgical techniques, assessing the risk of a temporary stoma and gathering a multidisciplinary team.

Ultrasound is an accurate test to diagnose urinary tract involvement in women with suspected pelvic endometriosis. Overall pooled sensitivity and specificity for detecting bladder DE on TVS is 55% and 99%, respectively[97]. Significant heterogeneity was found between reviewed studies in the meta-analysis and methodological quality was low[97]. Size of bladder DE may influence detection[98]. In a feasibility study on identification of the ureters in normal women (no endometriosis or anatomical distortion) during standard TVS, at least one ureter was identified in everyone and both ureters in 93%[99]. TVS is an attainable[100] and reliable tool for the diagnosis of pelvic ureteral involvement in cases of DE and additionally allows the detection of both the level and degree of obstruction[101]. Of note, the distal ureter, which is easier to visualize, may appear normal but stenosis may be present proximally or more cephalad. Endometriosis imaging should always include a renal ultrasound to exclude hydronephrosis. The presence of USL DE is an important TVS finding to consider, as it has been significantly associated with the presence of ureteral DE, and this knowledge can assist in surgical planning including consultation with urology services[102]. It is important that parametrial, paracervical and USL disease is visualized correctly on TVS and accurate terminology is used[103]. Disease in these locations makes surgery more complex and appropriate patient counseling is required due to the increased risk of complication such as postoperative bladder dysfunction.

Sonovaginography (SVG) is TVS combined with the introduction of saline into the vagina to act as an acoustic window between the probe and surrounding structures and was introduced by Dessole *et al.*[104] as a possible improved method to assess DE. In this study, SVG diagnosed posterior-compartment endometriosis more accurately than did TVS (sensitivity 90.6% *vs* 43.7%, specificity 85.7% *vs* 50.0%), and patient discomfort did not differ between groups[104]. Gel SVG, introduced by Reid *et al.*[105], is another important stand-off technique in which 20 mL of ultrasound gel is placed into the vagina for improved visualization of the posterior-compartment structures. For the detection of bowel DE, gel SVG demonstrated a sensitivity of 88% and specificity of 93%[105].

Another variant of contrast-enhanced TVS termed 'tenderness-guided' was introduced by Guerriero *et al.*[106,107]. This technique involves introducing more gel inside the ultrasound probe cover to increase the acoustic window and asking people to indicate which points are more painful under pressure. Their study demonstrated a sensitivity and specificity for detecting DE of 90% and 95% respectively, although a follow-up study, including more women, demonstrated high accuracy in detecting PVF endometriosis only and found the technique to have lower sensitivity in detecting anterior compartment, USL or rectosigmoid DE[107]. While placing more gel inside the probe cover offers an acoustic window, it also acts to cushion the probe, potentially decreasing ability to assess tenderness. Some believe that bowel preparation or rectal water contrast improves the detection of rectosigmoid DE by TVS. However, a review by Guerriero *et al.* included five studies specifically evaluating contrast-enhanced TVS in assessing rectosigmoid DE and overall, the review did not find statistical differences between the results of studies using enhanced *vs* non-enhanced TVS[75]. Conversely, Nisenblat *et al.* demonstrated higher DTA for TVS with bowel preparation and rectal water contrast in detecting rectosigmoid endometriosis compared with routine TVS[71]. Contrast enhancement may amplify the utility of 2D ultrasound in diagnosing DE, although further study is necessary. It should also be borne in mind that bowel preparation or rectal contrast may not be acceptable to all people.

There are benefits to ultrasound beyond its diagnostic accuracy. TVS provides a rapid result and is cost-effective compared to surgery and MRI[108]. In cases of advanced endometriosis, TVS performed according to the IDEA consensus can generate significant cost savings for healthcare systems if used in place of diagnostic laparoscopy[109]. TVS is generally thought to be acceptable to people, as per acceptability studies in early-to-mid-pregnancy and the ovarian cancer screening population[110–112], although no studies to our knowledge have assessed acceptability in an endometriosis population. Ultrasound is more than just a diagnostic test as it can help patients and clinicians to understand the extent and location of endometriosis by interpreting real-time tenderness and mobility, as well as facilitate objective monitoring of disease over time[113] and in many cases aid preoperative planning. People with endometriosis have reported that they appreciate seeing physical evidence of their 'invisible disease' in photographs and videos as this can validate their physical and psychological symptom experience[13]. TVS offers this visual evidence and facilitates counseling discussions regarding anatomy. Ultrasound is an important tool in the diagnostic work-up of possible endometriosis given its relatively high DTA, ability to predict disease location and extent, and ability to provide visual confirmation of disease, which can be therapeutic for patients at a psychological level.

Limitations. The most cited limitation of TVS in the diagnosis of endometriosis is its high false-negative rate, usually as a result of poor detection of SE[71,114]. However, a new diagnostic technique, SonoPODography, was introduced by Leonardi *et al.*[115] and is performed by instilling saline into the POD via an intrauterine balloon catheter to create an acoustic window between the ultrasound probe and surrounding structures (Figure 3). In diagnosing SE, this technique demonstrated a sensitivity of 64.9% and specificity of 100% with an NPV of 27.8%

and PPV of 100%. Performance of this test improved in those without DE, OE or obliteration of the POD[115], for example those with exclusive SE. While sensitivity is limited and as such, ruling out SE remains a challenge, the test does meet criteria for a triage test (sensitivity $\geq 50\%$ with specificity $\geq 95\%$), allowing disease to be ruled in with a positive result. This test, while optimistic, is more invasive compared with standard TVS and still warrants further validation in a larger trial, including external validation. In addition, fluid in the POD is insufficient to assess SE elsewhere in the abdomen and pelvis.

The accurate diagnosis of pelvic endometriosis by TVS or TRS may rely on the amount and location of disease. Holland *et al.* determined that the accuracy of TVS improved with an increasing total number of lesions up to a maximum of three, and sensitivity decreased with more extensive disease[116]. This suggests that, in more severe endometriosis, adhesions may obscure lesions more distant from the ultrasound probe, or that ultrasound operators are less likely to document smaller lesions when abundant[116]. In these cases of multiple deposits of endometriosis, and often, larger OE lesions, the anatomy can be extremely distorted, making it difficult to understand and map abnormalities systematically.

Although high levels of interobserver agreement have been demonstrated between experienced gynecological sonologists in diagnosing pelvic endometriosis[117], TVS performed by an untrained operator does not permit prediction of DE and specifically bowel involvement[118]. This likely limits the accessibility of high-quality ultrasound to larger tertiary referral centers where more experienced and subspecialized sonologists perform scans, although there is a steep learning curve to skill acquisition[82]. Ultrasound assessments performed by less experienced sonographers are more often falsely negative. This can impact disease trajectory greatly as people may be less likely to start treatment or receive further imaging or surgery with a negative ultrasound result.

Although ultrasound is typically considered non-invasive, like pelvic examination, TVS may not be acceptable to some people and may exacerbate pelvic pain symptoms. In those who decline TVS, TRS can be considered, and if conducted by an expert, can achieve equivalent or superior diagnostic performance compared with TVS[76]. However, many clinicians are uncomfortable with performing TRS and therefore non-performance of intracavitary ultrasound for endometriosis remains a real limitation.

Magnetic resonance imaging

MRI is often performed in suspected complex cases of endometriosis or before surgery because it is considered to be highly accurate[119]. The European Society of Urogenital Radiology (ESUR) performed an expert review to develop a MRI endometriosis protocol. It was found that more than 90% of MRI examinations performed for endometriosis were ordered to stage DE[120]. However, there is no consensus on how to report DE findings in detail on MRI, akin to IDEA for TVS. MRI can use various protocols (e.g. T1- and T2-weighted) and there is significant variability in the literature regarding the MRI protocols used in imaging endometriosis[120].

The ESUR guideline recommends that three 2D T2-weighted MRI sequences (sagittal, axial, oblique) be performed in the evaluation of DE. T1-weighted MRI sequences with and without fat suppression are recommended in the evaluation of adnexal endometriosis, although data are lacking in the use of T1-weighted MRI for evaluating DE. There is preliminary evidence to suggest that fat-suppressed T1-weighted MRI can be used in the evaluation of peritoneal endometriosis[121]. With regards to intravenous contrast (gadolinium), there is evidence to support its use in distinguishing OE from other hemorrhagic adnexal lesions and tubo-ovarian abscess[120]. The addition of gadolinium was not found to improve the detection of DE in the rectosigmoid, vagina or bladder[122]. The preparation for MRI involves fasting, bowel enema and a moderately full bladder[120].

Strengths. MRI allows evaluation in multiple planes, which can be advantageous in imaging multifocal, extrapelvic endometriotic lesions. Analysis of the images obtained can be performed subsequently and independently by (potentially off-site) expert radiologists, and all images appear the same to all viewers potentially allowing a more objective assessment. This is in direct contrast to sonography, which is dependent on expert-trained sonographers/sonologists who are geographically limited, and potentially costly and resource-intensive to train.

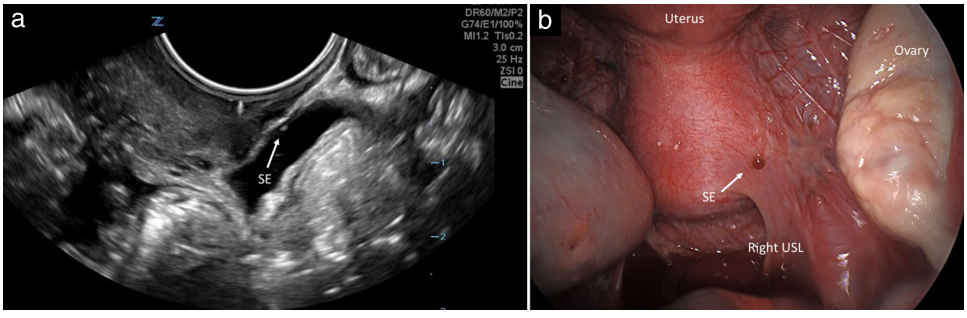

Figure 3 Transvaginal ultrasound (TVS) image (a) and corresponding laparoscopic image (b) showing superficial endometriosis (SE) on the right uterosacral ligament (USL). TVS was performed with infusion of saline in the pouch of Douglas (SonoPODography) to improve visualization. Note that additional SE lesions were visualized on laparoscopy which were not detected on preoperative TVS.

Nisenblat *et al.* reviewed seven studies (303 women) assessing the diagnostic accuracy of MRI for pelvic endometriosis (OE, SE, DE)[71]. The mean sensitivity and specificity were 79% and 72% respectively, which did not meet criteria for a replacement or triage test as compared to diagnostic laparoscopy. However, in the diagnosis of OE, three studies were reviewed and MRI met criteria for both a replacement test and triage test in ruling out OE. In assessing DE, MRI met criteria for a triage test to rule in endometriosis in the POD, vagina and rectosigmoid[71]. MRI has played a critical preoperative role in mapping the location of bowel endometriosis specifically in relation to the anal margin and associated deep lesions, although as mentioned above, TVS recently demonstrated this ability as well[95,96]. In a direct comparison study, Bazot *et al.* compared TVS, performed by an expert gynecologic radiologist, to MRI, interpreted by a gynecologic radiologist with 2 years of experience[54]. MRI was the most accurate method of diagnosing USL endometriosis (sensitivity 84.4%, compared to 78.3% with TVS) and vaginal endometriosis (sensitivity 80%, compared to 46.7% with TVS)[54]. A systematic review and meta-analysis analyzing the ability of TVS and MRI to diagnose DE demonstrated comparable diagnostic accuracy between the two modalities[123]. More recently, the diagnostic accuracy of TVS and MRI was evaluated in the mapping of DE using the IDEA consensus guidelines. MRI demonstrated higher accuracy for USL DE but TVS was superior for POD obliteration[124]. MRI performs well in detecting sacral nerve root DE[125], while no comparable data exist for TVS. Moreover, MRI can visualize extrapelvic lesions that are not visible with TVS.

Limitations. MRI is a static assessment and does not allow dynamic visualization of pelvic organ mobility, an important consideration for the gynecological surgeon. MRI may not estimate accurately the depth of penetration of endometriosis in the muscularis layer of the intestinal wall as it can be limited by artifacts caused by stool or intestinal peristalsis[119]. For this reason, the ESUR guideline recommends the routine use of an anti-peristaltic agent (glucagon or butyl-scopolamine), unless contraindicated, in the evaluation of DE[120]. SE is difficult to delineate on MRI and adhesions cannot be identified directly[126]. Further distance between MRI slices might also lower the detection rate. There is significant variability in the reported diagnostic accuracies of MRI for DE, likely due to differences in the imaging protocols used in various studies. For example, one review reported the sensitivity and specificity of MRI for diagnosing rectosigmoid endometriosis as 63–98% and 89–100%, respectively[119]. Additionally, there is variability in MRI reporting and more uncertainty in diagnosis for inexperienced readers[127]. The diagnostic confidence varies according to the location of endometriosis and identification can be difficult in the PVF and anterior compartment[127]. A study by Saba *et al.* demonstrated high inter- and intraobserver agreement in the identification of endometriosis in the ovary, rectosigmoid and RVS, whereas the agreement was suboptimal for USL endometriosis[128].

Following the ESUR recommendations, we believe that MRI should be used as a second-line technique in the diagnosis of endometriosis[120]. MRI is more costly and, in many centers, less accessible compared with TVS. Given that TVS performs comparably in the diagnosis of DE in the most recent review by Guerriero *et al.*[123] and is generally acceptable to patients, TVS/TRS should be the first imaging modality employed[129]. If uncertainties remain following advanced ultrasound techniques, or if endometriosis is out of the scope of TVS/TRS (e.g. cecal, sigmoid or diaphragmatic endometriosis), then MRI would be indicated. Ultrasound and MRI were evaluated as complementary imaging techniques in a prospective observational study and were together found to identify bowel DE correctly in 90.5% of cases[57]. In addition, if advanced ultrasound techniques are not available at a healthcare center, MRI may fill the void and act as a non-invasive diagnostic tool.

Relevance in DTA studies. Given the known differences in diagnostic accuracy outcomes between trained and untrained sonographers and radiologists, and the variability in experience levels employed in DTA studies, we presume a significant degree of heterogeneity in the reported accuracies of TVS and MRI in various studies. The size of lesions reported in studies is subject to inter- and intraobserver variability. A DE cut-off of ≥ 5 mm infiltration into the peritoneal tissue is limited by subjectivity in measurements both at the time of TVS and surgery. Moreover, sonographers may be calling SE 'deep' on imaging reports because there is a belief, based on current data[71], that SE cannot be diagnosed by TVS.

While SE has traditionally been considered a lesion < 5 mm in depth, it is not clear in all studies whether a cut-off of 5 mm is used when defining lesions and even when it is defined, it is not clear which imaging plane is used for measurement. In addition, there are likely differences in measurement methods between studies. It is even more difficult to measure lesions laparoscopically given the lack of granularity afforded by measurement with the naked eye. When an endometriotic lesion is excised or biopsied at the time of surgery, it inevitably also includes non-endometriotic tissue, which might result in overestimation of lesion size. This leads to inaccurate classification of endometriosis subtypes in DTA research, confounding the results. The decision in the recent International Terminology for Endometriosis[19] publication to remove lesion measurement from the classification may now simplify this issue. The potential influence of the time elapsed between use of a diagnostic test and the reference standard should also be considered, as well as our limited understanding of the natural history of endometriosis. It remains unclear whether SE progresses to DE over time or whether DE is an independent event[130].

In the context of DTA studies, the surgeon is in essence the gatekeeper of the 'reference standard' diagnosis. If a surgeon has not been blinded to preoperative investigations and a person was, for example, diagnosed with DE on imaging, they may err towards diagnosing DE on laparoscopy. Importantly, review articles on the

diagnosis of rectosigmoid DE discuss that there was no blinding of the surgeons to preoperative imaging in reviewed studies. This has the potential to inflate the diagnostic accuracy of laparoscopy, the gold standard test. Additionally, several reviewed studies reported complete POD obliteration secondary to endometriosis that could not be surgically cleared in all cases. Full surgical exploration of individuals with an obliterated POD is important for accurate diagnosis of bowel and USL DE and missing this diagnosis at the time of surgery may have negatively affected the validation of TVS/MRI[94]. Practically and ethically speaking, preoperative imaging findings are essential for guiding surgical techniques, making it difficult to design non-biased DTA research.

Surgical diagnosis

In the management of endometriosis, laparoscopy has a two-fold purpose and can be categorized into 'diagnostic' and 'operative' laparoscopy (Figure 4). Diagnostic laparoscopy involves visual diagnosis of endometriosis based on a wide variety of surgical appearances. Biopsies may or may not be taken of visually identified lesions for histological assessment, although biopsy is recommended as positive histology confirms the diagnosis. As outlined by the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project, high-quality diagnostic laparoscopy should include systematic evaluation of the uterus and adnexa, anterior abdomen, internal inguinal ring and inferior epigastric vessels, bladder dome, broad ligament, peritoneum of the ovarian fossae, vesicouterine fold, POD, pararectal spaces, rectum and sigmoid, appendix and cecum, small bowel, and diaphragm[131]. A 'close-tip' observation technique should be used with the laparoscope held at 2–5 cm from the tissue[131]. Operative laparoscopy is performed to surgically remove or ablate any endometriotic lesions or adhesions for symptomatic treatment. At the time of intended diagnostic laparoscopy, an operative procedure to treat disease may be performed only if time and surgeon skill permit and the disease is not severe enough to warrant the attention of a minimally invasive gynecological surgeon, colorectal surgeon, urologic surgeon and/or thoracic surgeon. When moderate-to-severe endometriosis is found, operative laparoscopy may be delayed so that adequate surgical expertise can be sought and the patient can be prepared appropriately and consent to treatment. The scenario of a two-stage procedure is not ideal for several reasons, including potential harm and inconvenience to the patient and significantly increased cost to the healthcare system[109].

Strengths. A systematic review was performed by Wykes *et al.* to determine the accuracy of laparoscopy in diagnosing endometriosis against the reference standard of histology and reported a sensitivity of 94% and specificity of 79%[51]. Since surgical visualization is currently considered the gatekeeper to histology (unless biopsies of normal-appearing areas are taken), these sensitivity and specificity values have been used as a cut-off when considering the potential value of less-invasive diagnostic tests in systematic review meta-analyses[71,132–134].

As discussed above, surgery offers people the opportunity to not only have their condition diagnosed but possibly treated. Abbott *et al.* performed a blinded study in which subjects were randomized to initially receive either a diagnostic or operative laparoscopy[135]. Operative laparoscopy was demonstrated to be more effective at reducing pain and improving QoL as compared to diagnostic laparoscopy[135]. A prospective study of women who underwent an operative laparoscopy for endometriosis demonstrated that the reduced pain and improved QoL

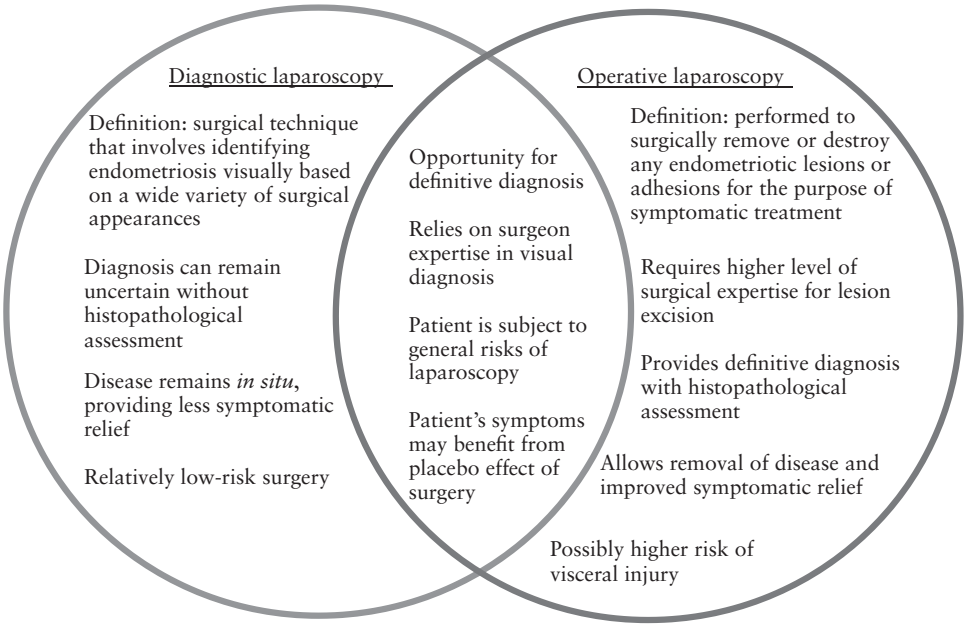

Figure 4 Comparison of diagnostic and operative laparoscopy in the treatment of endometriosis.

state persisted up to 5 years[136]. An observational study demonstrated that consistent peritonectomy in women with altered peritoneum followed by adjuvant hormonal therapy resulted in improved pregnancy outcomes and decreased disease recurrence[137]. In addition, there is a well-known placebo effect of laparoscopy in the management of endometriosis[135,138,139]. In Abbott *et al.*'s randomized trial, at 6 months, 30% of subjects within the placebo group reported symptomatic improvement. This placebo effect was found to affect all individual pain symptoms equally including dysmenorrhea, dyspareunia, non-cyclic pain and painful defecation[135].

Certainly, from a patient perspective, surgery is highly valued. A systematic review of the qualitative literature by Young *et al.* discussed that patients appreciated receiving a surgical diagnosis as they feel vindicated by having their disease visualized and photographed[13]. Additionally, patients were found to prefer surgical over medical management because surgical management was perceived to be associated with increased symptom relief and fewer side effects[13]. The opportunity for surgery to provide greater diagnostic potential, disease treatment and symptom relief cannot be understated.

Limitations. While the role of laparoscopy undoubtedly remains important in diagnosing and managing many people with endometriosis, it is important to consider the disadvantages of laparoscopy as the gold standard diagnostic tool. Frishman and Salak demonstrated that only one-third of women who undergo a laparoscopic procedure will receive a diagnosis of endometriosis, suggesting that many disease-free women are unnecessarily exposed to surgical risk and remain without a diagnosis[140]. This is partly secondary to persistently poor preoperative diagnosis of adenomyosis, an underestimated cause of pelvic pain, and challenges with diagnosing adenomyosis surgically. Laparoscopy has been associated with a 0.001% risk of vascular injury which may be life-threatening, a 0.16% risk of bowel injury and a 0.12% risk of urologic injury[141]. While there is value to ruling out endometriosis, people who undergo unnecessary laparoscopy not only incur surgical risks but may experience emotional consequences of negative surgery.

The reliability of laparoscopy as a diagnostic test for endometriosis is highly dependent on surgical experience and expertise in this area. Visual diagnosis of endometriosis may be complicated by heterogeneous or atypical lesion appearance, inaccessible lesions and interobserver variability. One study found that only 50% of laparoscopic biopsy specimens from areas suspicious for endometriosis were proven microscopically to be endometriosis[142]. In an analysis of the relationship between visual findings at laparoscopy and histological diagnosis, it was found that 25% of lesions labeled by surgeons as 'atypical-appearing tissue not presumed to be endometriosis' were confirmed as endometriosis histologically[143]. A recent study confirms the limitation of direct visualization with an overall accuracy of 77.1% (95% CI, 67.7–88.1%). Direct visualization has very poor specificity (40.0%; 95% CI, 21.1–61.3%) and NPV (58.8%; 95% CI, 36.0–78.4%)[144]. Amongst trained gynecological surgeons, it has been shown that endometriosis is less accurately diagnosed visually when lesions are black or red in color, small, superficial and disease is at an early stage (rASRM Stage 1)[145,146]. A recent study by Padmehr *et al.* analyzed the reliability of visual diagnosis of endometriosis and demonstrated particularly low interobserver ($\kappa = 0.157$) and intraobserver ($\kappa = 0.362$) agreement for SE[147]. Of note, the use of near-infrared fluorescence with indocyanine green has been proposed to allow proper localization of endometriotic lesions during surgery. Endometriotic lesions harbor extensive neovascularization causing tissue fluorescence with indocyanine green administration. This has been demonstrated to be effective in identifying endometriosis at laparoscopy, although mainly for patients with no previous abdominal surgery and low rASRM stage[148].

Considerable interobserver variability was demonstrated in surgeons' assessment of the number and location of endometriotic lesions and extent of disease by rASRM classification in a study of 108 gynecological surgeons who performed surgical video review[149]. As demonstrated in Figure 5, in cases of severe endometriosis with POD obliteration, visualization and biopsy of any disease may require extensive dissection, increasing the risk of visceral/vascular injury. Certainly, the ESHRE guidelines maintain that evidence is lacking that positive laparoscopy without histology proves the presence of disease[40]. Although these guidelines suggest that histological confirmation is always needed to verify a visual diagnosis of endometriosis, obtaining histological confirmation is not always possible, particularly in cases of extensive DE with POD obliteration, if the surgeon is untrained in advanced pelvic surgery.

While surgical diagnosis offers the opportunity for concomitant treatment, excision of advanced endometriosis requires specific surgical expertise. An inappropriate surgical approach may result in suboptimal treatment, which can lead to disease recurrence and pain, central sensitization, surgical complications and reduced fertility. The

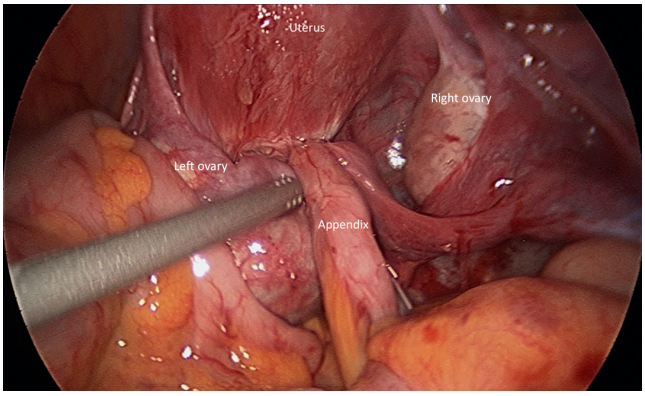

Figure 5 Laparoscopic image showing obliterated pouch of Douglas. While deep endometriosis can be assumed in this case, obtaining adequate visualization and tissue sampling for histology requires significant dissection, increasing the risk of operative complication.

level of surgical expertise in endometriosis surgery has been inversely correlated with inadvertent removal of healthy ovarian tissue at the time of OE excision[150], reducing ovarian reserve and potentially impacting future fertility[151]. Following surgical excision of endometriosis, it has been shown that 40–50% of women have recurrent disease at 5 years post surgery[152]. People with known suboptimal resections of endometriosis are at significantly increased risk of ongoing pain due to disease persistence as compared to those with complete disease excision[153]. Gynecologists should ethically consider their level of surgical expertise and ensure optimal preoperative planning, including staging with non-invasive imaging, before performing operative laparoscopy for endometriosis.

With the advancement of diagnostic imaging techniques, the number of people receiving needless surgery for diagnostic purposes should decrease. However, we should also begin to question the superiority of surgery over advancing imaging modalities in diagnosing endometriosis based on recent data. A well-designed diagnostic accuracy study by Goncalves *et al.*[154] assessed the performance of TVS with bowel preparation against diagnostic laparoscopy. Surgeons that were blinded to preoperative imaging and clinical data reviewed surgical videos from entry of the abdominal cavity until the completion of a systematic inspection (before any dissection began). TVS was able to detect retrocervical, ovarian and bladder endometriosis with similar sensitivity to diagnostic laparoscopy. Notably, diagnostic laparoscopy was unable to detect vaginal endometriosis, whereas it was detected on TVS with a sensitivity of 86% and specificity of 99% (compared against histology as reference standard). Diagnostic laparoscopy was considerably poorer at detecting rectosigmoid endometriosis with a sensitivity of only 3.7–5.6% compared with 96% for TVS[154]. Expert endometriosis surgeons and sonographers participated in this study. A novice sonographer may miss DE on TVS, while a novice gynecologist may still detect POD obliteration at laparoscopy, and thus laparoscopy could serve as a screen to triage referrals to an expert center. Conversely, it has also been demonstrated that general gynecologists may not recognize POD obliteration as well as advanced laparoscopic surgeons, indicating that expertise is necessary in recognizing a severe state of pelvic adhesions[78]. Figure 6 depicts bowel DE diagnosed on TVS and its corresponding laparoscopic appearance. One can appreciate the superiority of ultrasound, in this case, to characterize fully the size of the lesion. Given the limitations outlined here, high associated costs of surgery[108], typically long waiting times and growing body of DTA literature pointing to other diagnostic methods as potential replacement, triage or adjunctive tests, the appropriateness of surgery and histological confirmation as the ultimate or sole diagnostic tool is questionable.

Relevance in DTA studies. The reported diagnostic accuracy of laparoscopy may be clouded by several confounding factors. The systematic review by Wykes *et al.*[51] assessed diagnostic accuracy of visual diagnosis on laparoscopy as compared with the reference standard, histology. Of the 27 diagnostic test studies included in this review, only two involved pathologists blinded to the surgical diagnosis. In addition, it is not clear whether surgeons would have been blinded to the patient's clinical history, physical examination and preoperative imaging reports. In a clinical sense, lack of blinding makes these results more genuine as tests are seldom done in isolation and every result must be interpreted in the context of the pretest probability for a diagnosis. However, strictly speaking, the diagnostic accuracy of laparoscopy as reported in the literature is likely influenced by preoperative variables that affect the clinician's index of suspicion for endometriosis and may reflect combined accuracies.

Other surgical factors are relevant to DTA research. Surgical decisions may be tied to financial remuneration. In fee-for-service or self-pay/insurance models, surgical visualization and biopsy/excision of endometriosis may be valued more highly than simple diagnostic laparoscopy without biopsy. Most DTA studies take place during routine clinical care and are not funded by grant agencies outside of typical remuneration pathways for surgeons. Conversely, due to lack of skill, perceived risk or incomplete surgical consent, surgeons may refrain from sampling/excising tissue that appears to be endometriotic, which precludes histological confirmation, leaving readers to trust the surgeon (bearing in mind, PPV is imperfect, with many surgeon-diagnosed lesions not being confirmed histologically)[144]. In these cases, if other areas are biopsied, it may be assumed that the area not removed is also endometriosis, but this is not a guarantee. In studies that focus on lesion-specific DTA, this approach is limited.

Finally, in the opinion of the authors, it is inappropriate for DE to be first diagnosed at surgery. If a patient is diagnosed with rectosigmoid or urinary tract endometriosis

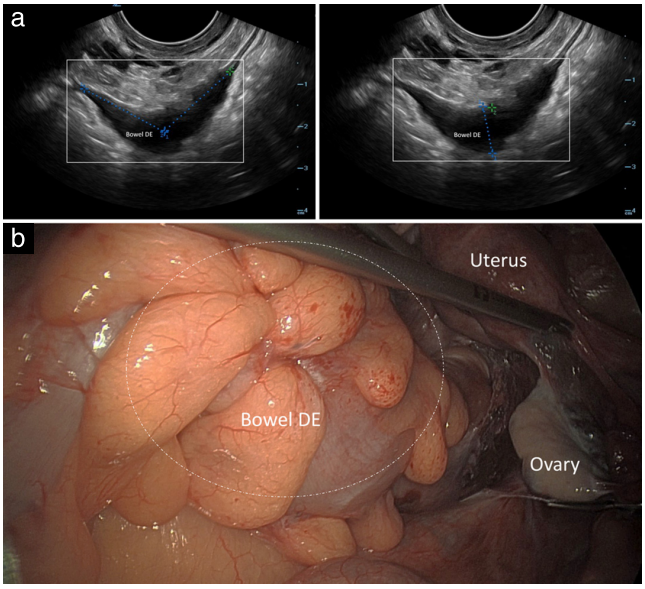

Figure 6 Diagnosis of deep endometriosis (DE) in the bowel on transvaginal ultrasound (a) and corresponding laparoscopic image (b). Note that the bowel exterior appears atypical, and the size and depth of the underlying endometriosis cannot be appreciated at surgery.

at the time of surgery, it does not allow for the requisite informed consent and surgical planning process to take place preoperatively. Even in the event that DE does not require excision (small lesion, asymptomatic), and the surgeon feels that they can visualize and diagnose endometriosis in hard-to-visualize areas (rectosigmoid, PVF), ideally histopathology should be obtained. It is not appropriate to biopsy areas such as the rectum without explicit consent.

Histology

A definitive diagnosis of endometriosis relies on histological assessment following tissue biopsy or excision. The histological diagnosis of endometriosis is based on the presence of endometriotic glands and/or stroma[155] in tissue specimens[156]. The presence of stromal arterioles, extravasated erythrocytes and pigmented histiocytes in or around the lesion may be a clue to the diagnosis, particularly when the endometriotic stroma is atrophic[156]. CD10 immunohistochemical staining of stromal cells can facilitate their recognition and support a diagnosis of endometriosis in problematic situations such as when biopsy material is limited or the glandular or stromal component is sparse or absent[157,158]. Endometriosis responds to circulating hormones and may demonstrate atrophic glandular changes in postmenopausal patients or those on oral contraceptives, danazol or progestins[156]. Endometriosis also demonstrates stromal decidualization during pregnancy[159,160] and, as recently reported by Ambrosio *et al.*, in response to progesterone therapy[161].

Strengths. Excision of lesions at the time of surgery facilitates histological analysis, allowing clinicians to confirm a diagnosis and rule out other conditions (often in the case of ovarian cysts). Histological evidence of endometriotic glands and/or stroma in a specimen is diagnostic of disease, and making this diagnosis is generally straightforward for the analyzing pathologist. There are no sensitivities or specificities available for this exam, as it is the highest level of confirmation with which to compare. Hurtado and Geber assessed the reliability of histological examination in endometriosis and demonstrated high interobserver ($\kappa = 0.78$) and intraobserver ($\kappa = 0.85$) agreement[162]. Through biopsy or excision of all suspicious areas, histology can confirm the location of endometriosis within the pelvis and disease extent. The ESHRE guideline for the management of those with endometriosis recommends that clinicians obtain tissue for histology during surgery for OE and/or DE to exclude rare cases of malignancy[40].

Histology may diagnose endometriosis even in the absence of visible disease. In a study by Khan *et al.*, normal-appearing peritoneum was biopsied in women with and without endometriosis, and occult microscopic endometriosis (OME) was found in 15% and 6% of subjects, respectively[163]. This study has, however, been critiqued for the methodology used (i.e. far viewing distance at time of laparoscopic lesion identification, size and location of biopsies taken), which may have contributed to their high rate of OME detection[164]. Gubbels *et al.* found OME in 39% of patients with clinically negative peritoneum on laparoscopy[165] and in the study by Gratton *et al.*, 58% (7/17) of people with visually normal pelvises had evidence of endometriosis on histology[144]. The ability of histology to detect endometriosis that is not visibly apparent makes it a remarkably valuable tool for diagnosis. Some gynecologists are advocating for routine full peritonectomy in people undergoing surgery for pelvic pain, partially for diagnostic purposes[166]. However, from a clinical perspective, it is crucial to consider the relevance of OME and whether its removal improves current symptoms or reduces future development of macroscopic disease, as peritonectomy and ureterolysis may confer surgical risk.

Limitations. Diagnostic problems can occur for the pathologist when the typical microscopic appearance of endometriosis is altered in both its glandular and stromal components. Characteristic features of the stromal component can be obscured by infiltration of histiocytes caused by menstrual changes and hemorrhage into endometriotic foci[156]. If laparoscopic biopsy samples are small, such as in cases of small SE lesions, specimens may only consist of endometrial stroma or may have thermal damage that precludes diagnosis. If such foci are not examined at high-power magnification, they can be misinterpreted as lymphoid tissue or non-specific findings[156]. Histological assessment also relies on accurate communication between the surgeon and pathologist to describe where the pathologist should look for endometriosis in larger sections. In addition, endometriosis can elicit a fibrotic reaction, particularly in old lesions. Fibrous obliteration can cause the amount of endometrial stroma to be sparse leading to difficulty in diagnosis[158]. Like other diagnostic modalities, correct diagnosis of endometriosis is dependent on the experience of the pathologist. Pathologists need to have a high index of suspicion and seek the presence of characteristic arterioles, foci of hemorrhage, histiocytes and CD10 immunoreactivity in these cases to confirm a diagnosis of endometriosis[156].

Correctly diagnosing endometriosis by histology may also be influenced by the surgical environment and method of resection. Exposure to cold, dry carbon dioxide may induce an inflammatory reaction in excised tissue, as demonstrated in an animal model[167]. Mechanical insult, such as crush injury at the time of surgery or grossing of pathology specimens, may result in artifactual displacement of tissue into vascular spaces, possibly confounding pathologic analysis. Thermal coagulation during cauterization may result in the formation of cautery granulomas, which appear as brown or black carbon pigment surrounded by histiocytes and multinuclear giant cells. Cautery artifact may or may not be associated with necrosis and these effects may additionally lead to diagnostic difficulty[156].

To our knowledge, there is no standardized method to prepare endometriosis specimens for pathologic analysis with regard to specimen sectioning. Lack of serial sectioning may lead to pathologists missing small

Table 1 Summary of strengths, limitations and reported diagnostic accuracy of various diagnostic methods for endometriosis

Diagnostic modality	*Strengths*	*Limitations*	*Diagnostic accuracy*
Clinical history	• Non-invasive • Feasible, low-cost • Symptomatology can predict disease location • May facilitate therapeutic alliance • May guide treatment choice, depending on complaints	• Common symptoms of endometriosis have wide differential diagnosis • Symptoms not predictive of disease extent	Sn, 76–98%[44,45]; Sp, 20–58%[44,45]
Physical examination	• Accessible • High specificity • Opportunity to detect DE by visualization or palpation	• Low sensitivity • Outcomes are operator-dependent • Diagnostic accuracy varies by disease location • Examination may be considered invasive and painful	Sn, 18–88%[28,44,54]; Sp, 76–100%[28,44]
Biomarkers	• Objective measure • Combination may rule in endometriosis as a triage test (further research required)	• Dependent on laboratory techniques and quality control protocols • Some vary with hormonal and menstrual fluctuations • Some are not specific to endometriosis • Cannot discern DE, OE or SE	Anti-endometrial antibodies: Sn, 81%; Sp, 75%[133] IL-6: Sn, 63%; Sp, 69%[132] CA 19-9: Sn, 36%; Sp, 87%[132] CA 125: varies by cut-off used[132]
Ultrasound	• High specificity and sensitivity for OE • Overall high accuracy in detecting DE and POD obliteration • Dynamic nature for organ mobility • Allows anatomic mapping • Opportunity to provide visual evidence to patients • High tolerability • Cost-effective	• Limited ability to detect SE • Detection of DE requires highly trained sonographers/sonologists • Outcomes are operator-dependent • Examination may be considered invasive and painful	SE: Sn, 65–79%; Sp, 91–95%[71] OE: Sn, 93%; Sp, 96%[71] DE: Sn, 79%; Sp, 94%[71]
MRI	• Images obtained appear the same to all viewers • Overall high accuracy in detecting DE and extrapelvic endometriosis • Allows anatomic mapping • Opportunity to provide visual evidence to patients	• Static assessment • Limited ability to detect SE • Variable imaging protocols reported in literature • Low accuracy in defining bowel depth of invasion • Requires specific training endometriosis • No consensus on how to describe findings • High cost compared with ultrasound	SE: Sn, 79%; Sp, 72%[71] OE: Sn, 95%; Sp, 91%[71] DE: Sn, 94%; Sp, 77%[71]
Laparoscopy	• Overall high accuracy, considered gold standard • Allows concomitant diagnosis and treatment • Opportunity to provide visual evidence to patients • Significant placebo effect	• Invasive, carries surgical risk • Diagnostic accuracy dependent on surgical experience • Visual diagnosis challenged by heterogeneous lesion appearance, inaccessible lesions	Sn, 90–94%[49,51,141,144]; Sp, 40–79%[51,144]
Histology	• Ultimate confirmation of diagnosis • Can rule out other conditions • Can diagnose without visual confirmation	• Obtaining tissue for histology requires surgical excision • Influenced by surgical environment and method of resection	Not available

DE, deep endometriosis; MRI, magnetic resonance imaging; OE, ovarian endometriosis; POD, pouch of Douglas; SE, superficial endometriosis; Sn, sensitivity; Sp, specificity.

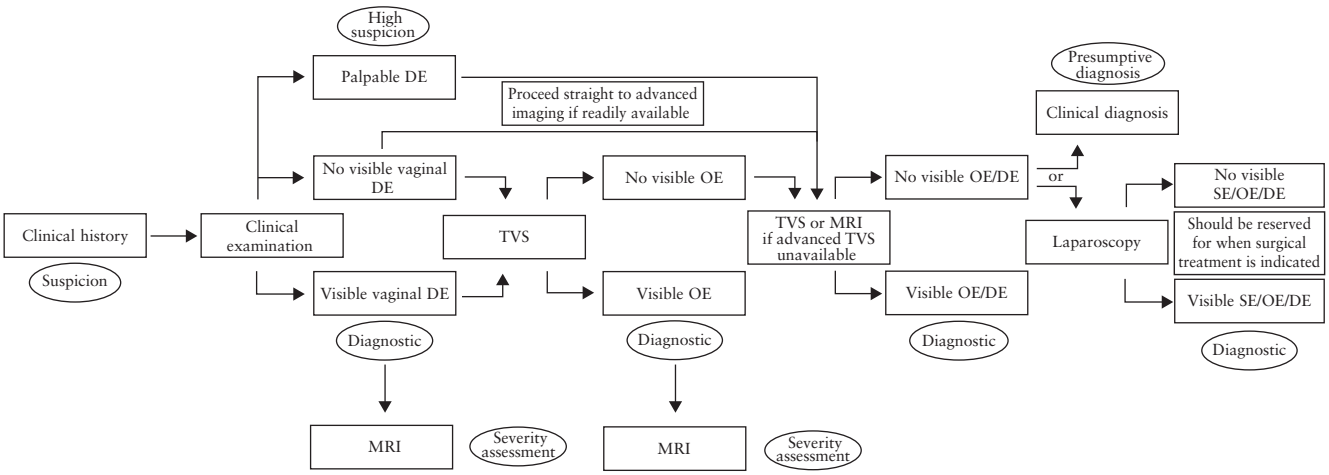

Figure 7 Flow diagram outlining proposed multipronged approach for diagnosis of endometriosis. DE, deep endometriosis; MRI, magnetic resonance imaging; OE, ovarian endometriosis; SE, superficial endometriosis; TVS, transvaginal ultrasound.

lesions in mild disease. In a study evaluating the detection of appendiceal endometriosis in women undergoing surgery for CPP, a modified pathologic analysis protocol involving serial sectioning and complete evaluation of the appendix and mesoappendix resulted in significantly higher rates of endometriosis diagnosis[168]. Thus, while the diagnosis of endometriosis ultimately relies on histological examination, limitations to pathologic assessment need to be considered.

Relevance in DTA studies. Visual diagnosis at the time of laparoscopy remains the gatekeeper to histologic diagnosis, and as discussed previously, visual diagnosis is imperfect. Understanding the DTA of histology in endometriosis is limited as it is difficult to compare cases of endometriotic-appearing tissue to controls when routine biopsy is not performed. In line with the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project[131], we advocate for standardized collection of biopsies at the time of laparoscopy in people undergoing surgery for possible endometriosis, even when no disease is seen, for both clinical and diagnostic research purposes.

CONCLUSIONS

The diagnosis of endometriosis remains a challenge despite years of investigation and research in this area. While many clinicians continue to rely on surgical and histological confirmation to diagnose endometriosis, we highlight here that all methods of diagnosis are imperfect and subject to limitations. On the other hand, all methods have strengths. The strengths, limitations and reported sensitivities and specificities of diagnostic methods for endometriosis are summarized in Table 1. Although non-invasive diagnostic methods, such as clinical assessment, biomarkers and imaging, have not yet qualified as replacement tests for surgery in diagnosing all types of endometriosis in the DTA literature, these methods may be sufficient in many clinical scenarios to provide people with a 'rule-in' diagnosis. Indeed, we advocate for a multipronged approach to diagnosing endometriosis rather than upholding the doctrine that the gold standard is surgery and histology (Figure 7). When possible, people with suspected endometriosis should be referred to a specialized tertiary center, not only for surgical management but also for non-invasive imaging diagnosis. While we recognize that our work is limited by a lack of systematic methodology, this State-of-the-Art Review provides readers with a basis to consider the strengths and limitations of each diagnostic method in individual patient scenarios. General practitioners and gynecologists lacking the resources to perform appropriate examinations or diagnostic tests should refer patients with suspicion of endometriosis to specialized centers to facilitate timely diagnosis.

DISCLOSURES

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Evaluation of biomarkers as a diagnostic tool for endometriosis

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Fortalezas y limitaciones de las herramientas de diagnóstico de la endometriosis y su relevancia en la investigación sobre la precisión de las pruebas de diagnóstico

RESUMEN

La endometriosis es una enfermedad sistémica crónica que puede causar dolor, infertilidad y reducción de la calidad de vida. El diagnóstico de la endometriosis sigue siendo un reto, lo que provoca retrasos en el diagnóstico de las pacientes. La investigación sobre la precisión de las pruebas diagnósticas en la endometriosis puede ser difícil debido al sesgo de verificación, ya que no todas las pacientes con endometriosis se someten a pruebas diagnósticas definitivas. El objetivo de esta revisión de las técnicas de vanguardia es proporcionar una actualización exhaustiva de los puntos fuertes y las limitaciones de las modalidades de diagnóstico utilizadas para la endometriosis y discutir la relevancia de la investigación sobre la precisión de las pruebas de diagnóstico correspondientes a cada una de ellas. Se realizó una revisión exhaustiva de la literatura sobre los siguientes métodos: evaluación clínica que incluya el historial y el examen físico, biomarcadores, diagnóstico por imágenes, diagnóstico quirúrgico e histopatología. Esta revisión sugiere que, aunque los métodos de diagnóstico no agresivos, como la evaluación clínica, la ecografía y la imagen por resonancia magnética, todavía no se pueden considerar formalmente como pruebas que sustituyan a la cirugía en el diagnóstico de todos los subtipos de endometriosis, es probable que sean adecuados para los estadios avanzados de la endometriosis. También se demuestra en esta revisión que todos los métodos tienen fortalezas y limitaciones, lo que lleva a la conclusión de que no debería haber un único método de diagnóstico de referencia para la endometriosis, sino más bien múltiples métodos de diagnóstico aceptados y apropiados para las diferentes circunstancias.

子宫内膜异位症诊断工具的优势和局限性以及在诊断测试准确性研究中的相关性

摘要

子宫内膜异位症是一种慢性系统性疾病，会导致疼痛、不孕和生活质量下降。该疾病的诊断仍然具有挑战性，因此患者的症状出现很长时间以后才能做出诊断。由于证实偏倚，对子宫内膜异位症进行诊断测试准确性研究可能会非常困难，因为并非所有的子宫内膜异位症患者都接受明确的诊断测试。本最新文献综述旨在全面更新子宫内膜异位症采用的诊断模式的优点和局限性，并探讨每种诊断模式有关诊断测试准确性研究的相关性。本研究对以下方法进行综合性的文献综述：临床评估，包括病史和体检、生物标志物、影像诊断、手术诊断和组织病理学。结果表明，虽然非创伤性诊断方法（如临床评估、超声和磁共振成像）暂无资格成为正式诊断所有亚型子宫内膜异位症的替代手术检查方法，但很可能会适用于子宫内膜异位症的晚期阶段。文献综述还能证明所有方法都有其优点和局限性，因此本研究得出结论：子宫内膜异位症不应有单一黄金标准诊断方法，而应具有适合不同情况的多种公认诊断方法。