Diagnostic Accuracy of Transvaginal Ultrasound in Women with Endometriosis at Deeply Infiltrating, Ovarian, and Superficial Peritoneal Sites

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A Capstone Paper submitted to the faculty of
the University of North Carolina at Chapel Hill
in partial fulfillment of the requirements
for the degree of Master of Health Sciences
in the Physician Assistant Program

Chapel Hill

December 2019

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11/14/2019

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11/14/2019

Introduction

Endometriosis is a multifaceted disease that is associated with dysmenorrhea, noncyclic pelvic pain, dyspareunia, and infertility [1]. It affects approximately 1 in 10 women, up to 200 million worldwide, and can disrupt every aspect of a woman's life, including sexual relationships, appetite, sleep, exercise, work productivity, and emotional well-being [2]. When extrapolated, endometriosis is a disease that has a high cost to both patients and society as a whole, as patients incur personal charges related to pain control and infertility management, while absenteeism and loss of productivity contribute to lost earnings worldwide [3]. Despite the disease's prevalence and devastating effects on a woman's life, the average time from symptom presentation to endometriosis diagnosis is 8-12 years, a conservative estimate when considering most women with the disease will never be diagnosed [3]. This delay in diagnosis and treatment has been shown to cause an increase in long term disease sequelae, significant degradation in the patient-provider relationship, and further progression of the disease [2,4].

The cause of this unfortunate delay in diagnosis is multifaceted. A large narrative review evaluating the social and psychological impact of endometriosis on women's lives found that the average time between a woman's initial symptoms and initial presentation for evaluation was 3.7 years. Many causative social factors were cited, including difficulty perceiving the difference between normal and pathologic symptoms, viewing menstruation as shameful or needing to be hidden, and reinforcement of symptom concealment from male and female peers [4]. The average delay from initial clinical presentation to diagnosis was between 3.7 and 5.7 years. Factors contributing to medical delay of diagnosis included referral delay, misdiagnosis, and lack of provider knowledge, all of which contributed to women feeling ignored or dismissed by providers[4]. A significant number of women reported feeling relieved, legitimized, and often angry at the delay after receiving an endometriosis diagnosis, all of which have been shown to contribute to a degradation in the patient-provider relationship. After diagnosis, women report negative impacts to many aspects of their lives, including intimate relationships, work and productivity, social lives, family planning, fertility, sleep quality, and mental health [4].

At this time, laparoscopy with histologic sampling is the only tool available for definitive diagnosis. Due to its cost and inherent risks, this tool is out of reach for many patients, especially those that do not have access to a tertiary gynecologic referral center. A less invasive diagnostic tool could shorten time to diagnosis, help preserve patient-provider relationship, and potentially

allow the diagnosis to be made in the primary care setting [3]. Transvaginal ultrasound is a low-cost, highly available tool that has shown significant utility in diagnosing many causes of pelvic pain [5]. This narrative review will seek to evaluate the current research on the diagnostic capability of transvaginal ultrasound (TVUS) for diagnosing endometriotic lesions at ovarian, superficial peritoneal, and deeply infiltrating sites. If accuracy is high enough, TVUS as a less invasive, less expensive tool for diagnosis could allow providers to evaluate patients for endometriosis earlier in their disease, increase quality of patient care, and decrease associated costs incurred by both the patient and the health care system.

This narrative review will begin with an overview of the natural history of endometriosis, including epidemiology, pathophysiology, clinical manifestations, current available treatments, and diagnostics. This will be followed by an evaluation and discussion of the current research on the diagnostic accuracy of TVUS in the diagnosis of endometriosis. The primary outcome will be to analyze whether TVUS can accurately diagnose ovarian, superficial peritoneal, and deeply infiltrating endometriosis when compared to laparoscopy with histologic examination.

Background

Epidemiology

Many patients with endometriosis will experience either no symptoms or mild symptoms that may be considered within the normal realm of menstrual-related symptoms. This makes identifying the prevalence of endometriosis quite difficult [3]. Various studies that have sought to determine the general population prevalence have produced highly variable results ranging from 1% to 15%, with approximately 10% being the accepted value [2]. For women with symptomatic presentation, prevalence has been reported up to 70% when the presentation includes pelvic pain and 50% when the presentation includes infertility [6]. There appears to be a genetic association, as women with first degree female relatives affected by the disease have a higher likelihood of being diagnosed with endometriosis [7]. Factors that increase a woman's risk for endometriosis include being nulliparous, early menarche, menstrual cycles shorter than 27 days, menorrhagia, height over 68 inches, and low BMI [8]. Conversely, protective factors include cycles longer than 27 days, late menarche, multiparity, and extended periods of lactation. White or caucasian race appears to increase a woman's risk, but there is limited evidence to support this [8].

Pathophysiology

By definition, endometriosis is the presence of endometrial tissue outside of the uterus. The pathogenesis of the disease likely includes genetic factors, autoimmune dysregulation, and abnormal endocrine signaling, in addition to the presence of ectopic endometrial tissue [9]. The ectopic endometrial tissue implants, grows, and causes an inflammatory reaction which can lead to scarring and anatomic dysmorphism [8]. The exact cause of these ectopic implants is poorly understood. A 2014 meta-analysis of 8 papers analyzed genetic data from a total of 11506 endometriosis cases showed that six genetic loci were significantly associated with endometriosis [7]. However, analyses have failed to identify a genetic marker consistently associated with the disease.

The leading theory for the pathogenesis of ectopic endometrial tissue implantation is retrograde menstruation, in which endometrial tissue flows backward through the fallopian tubes and into the abdomen during menstruation [8]. However, there is uncertainty surrounding this theory, as up to 90% of women have been shown to have retrograde menstruation and endometriosis has been diagnosed in prepubescent girls [7].

After implantation, the endometriotic implants cause pain through inflammatory and neurologic responses. A variety of inflammatory markers are involved in the inflammatory process, with prostaglandins being the primary culprit [9]. The implants have also been shown to cause surrounding changes to sympathetic and sensory nerve fibers, with some studies showing endometriosis patients to have a higher density of nerve endings within and around implants [9]. This suggests another possible genetic link to endometriosis symptoms, as a predisposition to higher inflammatory markers or increased nerve endings could increase pain signaling and symptoms [7].

The pathogenesis for infertility or subfertility caused by endometriosis is thought to correlate with the stage of the disease, with a greater burden of disease associated with more inflammatory markers and more scar tissue [9]. This increase in inflammatory markers can lead to ovarian or endometrial hormonal dysfunction, which is thought to cause a subprime environment for ovulation, fertilization, and implantation of a zygote. This dysfunction can occur at any stage of endometriosis, including early, minimally-invasive disease, although the process remains poorly understood [8]. As the disease progresses, more deeply infiltrating lesions can lead to

significant scarring, adhesions, and subsequent pelvic anatomic dysmorphism. This is also thought to lead to a hostile and non-ideal environment for fertility [8].

Clinical Manifestations

Endometriotic lesions can implant in a variety of locations, both pelvic and non-pelvic. Figure 1 demonstrates common locations of pelvic endometriosis, but does not depict endometriosis outside of the pelvis [10]. These locations most commonly include the ovaries, anterior or posterior uterine cul-de-sac, any of the uterine ligaments, the uterus itself, the fallopian tubes, and the sigmoidal bowel [9]. A majority of patients present with lesions in more than one location, with the ovaries being the most common. In rare cases, endometriotic lesions have been diagnosed in locations including the breast, thorax, lung, central nervous system, and abdominal organs. This can represent diagnostic challenges, as the symptoms associated with lesions in rare locations can be nonspecific and intermittent [3]. When a lesion is located within the pelvis, it is classified into one of three categories: ovarian, superficial peritoneal, or deeply infiltrating. Ovarian lesions occur on the ovaries, superficial peritoneal lesions are less than 5mm into the peritoneum, and deeply infiltrating lesions are 5mm or more deep into the peritoneum [8].

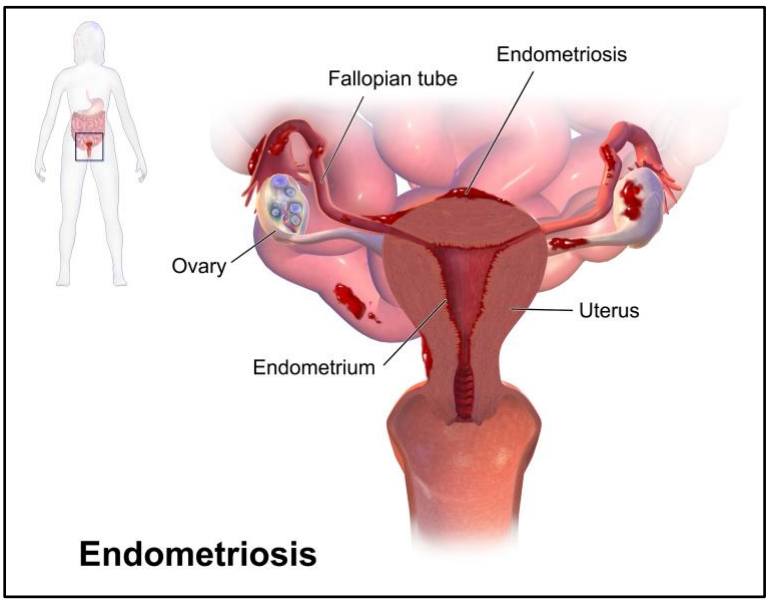

Figure 1. Pelvic endometriosis, UNC Center for Endometriosis

The most common presenting complaints of women with endometriosis are pelvic pain, infertility, and ovarian mass [3]. The majority of patients present with some complaint of pain, which can include dysmenorrhea, noncyclic pelvic pain, dyspareunia [pain with sex], dyschezia [pain with defecation], and dysuria. There is generally a direct association between the location of endometriotic lesions and the symptoms experienced. However, a patient's symptom burden is not necessarily correlated with disease burden [3]. For example, one patient may present with severe pain but only have two to three superficial lesions, while another patient may present with

mild pain but have 10+ deeply infiltrating and superficial lesions with severe scarring [2]. This represents another diagnostic challenge, and demonstrates the importance of practitioners maintaining a high degree of suspicion in patients presenting with any degree of chronic pelvic pain.

Current Treatment Options

There is no cure for endometriosis; rather, the current treatment options rely on symptom management. Treatment plans typically involve a two-fold approach utilizing both medical and surgical modalities. The first line medical therapy for endometriosis-related pain are non-steroidal anti-inflammatory drugs (NSAIDs).[11] These medications are particularly well-suited to combat the prostaglandin mediated pain caused by endometriosis because of their anti-prostaglandin properties. NSAIDs are also generally very safe and well-tolerated, making them a great option for most women [11]. Combined oral hormonal contraceptive (COCs) medications are another option for the management of endometriosis-related pain, particularly the pain associated with menstrual cycles. By regulating the menstrual cycle and making a patient's periods lighter, shorter, and more regular, COCs can decrease the pain associated with menstruation[11]. COCs are also generally safe and well-tolerated by most populations. If NSAIDs and COCs are ineffective at managing pain, medications such as GnRH agonists, Danazol, and aromatase inhibitors are further options. These medications work in different ways to reduce the effects of estrogen in a woman's body, including suppressing menstruation and associated pain, but they generally have more side effects and are less well tolerated than first line treatments[11].

The medical treatment of endometriosis-related infertility is similar to the approach to infertility treatment in patients without endometriosis. The mainstay of medical treatment is clomiphene citrate (Clomid), a medication that stimulates follicle growth and ovulation[12]. The addition of gonadotropins and aromatase inhibitors can also be used to enhance follicle stimulation. The next step in medical assistance in infertility is the use of assisted reproduction technology (ART). This includes In-Vitro Fertilization (IVF) and Intrauterine Insemination (IUI) [12]. Despite these methods, a diagnosis of endometriosis significantly increases a woman's probability of treatment failure compared to women without endometriosis [12]. Progression of the disease is shown to be directly related to the probability of failure, with greater severity of disease conveying greater risk of IVF failure [12].

The surgical management of endometriosis related pain and infertility are similar. Surgical management for infertility focuses on correcting distorted pelvic anatomy in women with moderate to severe disease [12]. Unfortunately, this approach has not been validated in RCTs and the fertility benefit from surgery is unclear. However, laparoscopic removal or ablation of lesions has been shown to significantly reduce pain symptoms in women with mild and moderate symptoms [11]. While there is a high return to surgery rate (over 50% at the seven year mark), multiple RCTs have demonstrated a benefit to removing lesions at the time of laparoscopic diagnosis. This is a major strength of laparoscopy, in that it can be both diagnostic and therapeutic. Other surgical options for pain management include removal of ovarian endometriomas, neurectomy, and hysterectomy with bilateral salpingo-oophorectomy [11]. The latter is viewed as a last-resort option for women with debilitating symptoms who have failed other therapies and do not desire child-bearing. Even after hysterectomy, disease recurrence is still possible and many patients do not achieve complete pain relief. [13]

Diagnosis

For definitive diagnosis of endometriosis, surgical biopsy with histologic review remains the gold standard [14]. This has been the case since the early 20th century. The current standard surgical technique is laparoscopy [14]. One benefit from this technique is that it can be both a diagnostic and therapeutic procedure. This can be helpful if a patient desires surgical management for their disease. However, despite years of research, there is no noninvasive diagnostic test available [2]. Some experienced providers may be comfortable managing the disease symptomatically without a surgical diagnosis, but many primary care providers do not have sufficient gynecology training to feel comfortable with this [2]. This is a significant reason why most women will go years without a definitive diagnosis for their endometriosis symptoms. At least part of this diagnostic and symptomatic burden could be relieved with a noninvasive diagnostic test [2]. Research is currently being conductive in a variety of outlets, including transvaginal ultrasound (TVUS), transrectal ultrasound (TRUS), and serum biomarkers. TVUS currently has the most promise and the most research available as a potential diagnostic test for the most common endometriosis locations, and will be the focus of this narrative review.

Methods

A thorough online search was conducted through PubMed, Google Scholar, and The Cochrane Library of Systematic Reviews. The search terms ‘endometriosis AND ultrasound

AND deep,' 'endometriosis AND ultrasound AND ovarian,' and 'endometriosis AND ultrasound AND superficial' were used. To be included in this review, studies needed to be systematic reviews, published since January 1st 2009, evaluate human subjects, include no author overlap with other studies, and compare TVUS at ovarian, deeply infiltrating, and/or superficial peritoneal endometriosis against laparoscopy with biopsy. Reviews including pregnant patients were excluded. For superficial peritoneal endometriosis, the criteria were broadened to include primary research due to a lack of systematic reviews evaluating superficial endometriosis. From this broadened criteria, 51 studies resulted. To prevent overlap of patient data within reviews, only the most recent, relevant paper for each lead author was evaluated. A list of excluded studies and the reasons for exclusion can be found in Appendix 1. The four final studies selected for this paper were chosen based on relevancy to the clinical question of this paper, methodologic quality, and assessment by the "A MeaSurement Tool to Assess systematic Reviews 2" (AMSTAR 2) criteria and the "Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS 2) tool. A table of the AMSTAR 2 and QUADAS 2 evaluations is found in Appendix 2 and Appendix 3.

Results

Out of the search and evaluation, two systematic reviews and two diagnostic accuracy studies were identified as eligible, relevant, and of good methodological quality in the evaluation of TVUS diagnostic accuracy of endometriosis at deeply infiltrating (DIE), ovarian, and superficial peritoneal sites. Details on each paper's features, risk of bias, and methodologic quality is available in Table 1. Statistical results from each paper were identified and are listed in Table 2, along with the endometriosis locations that were evaluated.

Table 1. Strengths, limitations, and risk of bias for each paper

Study	Study Type and Set-Up	Strengths	Limitations	Risk of Bias
Guerriero et. al, 2018. Transvaginal ultrasound vs magnetic resonance imaging for diagnosing deep infiltrating endometriosis: systematic review and meta-analysis.	Systematic review with statistical meta-analysis of data from head-to-head clinical trials comparing MRI and TVUS in diagnosing DIE	Relatively high number of subjects in analysis (n=424), studies within review all have the same head-to-head set up	Limited number of studies available for analysis, moderate heterogeneity of study participants and results	Based on AMSTAR 2 Criteria, unclear risk of bias; authors do not declare conflicts of interest, sources of funding, or list of excluded studies. Full evaluation in Appendix 2.
Nisenblat et. al, 2016: Imaging modalities for the non-invasive	Systematic review using Cochrane methods to assess the diagnostic accuracy of	Large review (49 articles and 4807 participants), very high methodological quality	High heterogeneity between studies, small sample sizes within studies,	Based on AMSTAR 2 Criteria, unclear risk of bias given authors do not list complete list of

diagnosis of endometriosis.	imaging tools in the diagnosis of endometriosis	(extensive details for methods, results, and discussion sections), extensive statistical analysis	high/unclear risk of bias for each study	excluded studies; however, in setting of high volume of studies evaluated and the authors listing reasons for exclusion, would consider a low risk of overall bias given comprehensive and detailed review otherwise. Full evaluation in Appendix 2.
Reid et. al, 2019. The association between ultrasound-based "soft markers" and endometriosis type/location: A prospective observational study.	Multicenter prospective observational study. Participants with chronic pelvic pain were recruited from tertiary gynecologic referral centers, then underwent TVUS, history, and laparoscopy. Primary results included correlation between test results and accuracy of TVUS findings in predicting location of endometriosis	Findings are consistent with previous studies with similar objectives, highly detailed description TVUS "soft-markers" involved in the study	Small sample size, high potential for referral bias, non-standardized format for history taking, potential for subjective reporting from sonographers, unclear if surgeons were blind to TVUS results	Based on the QUADAS-2 tool, there is a low risk of bias in patient selection, index test, and flow and timing. There is an unclear risk of bias in the reference standard. There is low concern regarding applicability. Full evaluation in Appendix 3.
Chowdary et. al, 2018. Multicentre retrospective study to assess diagnostic accuracy of ultrasound for superficial endometriosis-Are we any closer?	Retrospective analysis of women who received TVUS and laparoscopy in their work-up for endometriosis. Women found to have isolated superficial endometriosis were included in analysis, with primary objective to determine accuracy of TVUS in detecting superficial endometriosis.	Single sonographer for TVUS assessment, highly detailed description of imaging protocol	Small sample size, retrospective analysis, limited statistical analysis, subjective assessment by sonographer could limit reproducibility	Based on the QUADAS-2 tool, there is a low risk of bias in patient selection, index test, reference standard, and flow and timing. There is low concern regarding applicability. Full evaluation in Appendix 3.

Quality Assessment of Diagnostic Accuracy Studies-2 Tool: [15]*, A MeaSurement Tool to Assess systematic Reviews-2 Criteria:* [16]

Deeply Infiltrating Endometriosis

Guerriero et. al is a systematic review with meta-analysis that examines and compares the accuracy of transvaginal ultrasound (TVUS) and MRI in the diagnosis of deeply infiltrating endometriosis (DIE) [17]. A total of six studies (n=424) were considered eligible, in that all of the study's participants received TVUS, MRI, and laparoscopy (the criterion standard) in the evaluation for endometriosis. For the purposes of this narrative review, only the TVUS results were examined. The authors broke down their evaluation into specific locations for DIE. Specifically, they examined the rectosigmoid, rectovaginal septum, and uterosacral ligaments, three of the most common locations for DIE. For the rectosigmoid, the pooled sensitivity and specificity of TVUS was found to be 0.85 and 0.96 respectively. For the rectovaginal septum,

pooled sensitivity and specificity of TVUS was found to be 0.59 and 0.97 respectively. For the uterosacral ligaments, pooled sensitivity and specificity of TVUS was found to be 0.67 and 0.86 respectively. The results are detailed further in Table 2, including confidence intervals. For all locations, heterogeneity was found to be moderate to high through the Cochran's Q-statistic and the I_2 index. Meta-regression was performed on sample size, prevalence, median patient age, number of observers (single/multiple), index test description and reference standard description. The authors were unable to find an explanation for the heterogeneity. The authors also did not provide a total sensitivity or specificity value for all locations of DIE. Overall, the authors concluded that TVUS has valuable diagnostic capability and should be a first line technique for evaluating DIE.

Nisenblat et. al conducted a systematic review evaluating and comparing the diagnostic capabilities of a variety of noninvasive tests for diagnosing endometriosis [8] with the laparoscopic and histologic sampling standard. This included TVUS, TRUS (trans-rectal ultrasound), MRI, and biomarkers. For the purposes of this narrative review, only data involving TVUS was evaluated. The authors' criteria for a test to be considered a replacement diagnostic test for laparoscopy is sensitivity 94% or above and specificity 79% or above. For a test to be considered a study specified "SpPin" rule-in triage test, sensitivity needed to be 50% or above and specificity 95% or above. For a test to be considered a study specified "SnNout" rule-out triage test, sensitivity needed to be 95% or above and specificity 50% or above. Through a meta-analysis of 49 studies including 4807 women, the authors found that TVUS met criteria as a SpPin triage test for evaluating DIE at the uterosacral ligaments, rectosigmoid, rectovaginal septum, vaginal wall, and the Pouch of Douglas. It failed to meet criteria as a replacement diagnostic test. The authors note significant heterogeneity between papers for most of the results. The results are detailed further in Table 2, including confidence intervals.This was assessed through visual examination of forest plots and co-variate testing when more than 10 studies were available for a specific diagnostic test. In these cases, the authors were unable to identify the cause of heterogeneity.

Ovarian Endometriosis

Nisenblat et. al included 10 studies that specifically evaluated the diagnostic capability of noninvasive tests in the evaluation of ovarian endometriosis [8]. Data from these 10 studies plus information on ovarian endometriosis from the 39 additional studies was compiled in a meta-

analysis for this evaluation. Using the same criteria as described in the deeply infiltrating endometriosis subsection of the results section, the authors found that TVUS met criteria as a SpPin triage test (Sn 50% or above, Sp 95% or above) for ovarian endometriosis, in that a positive test can rule-in the presence of endometriosis at that location. It failed to meet criteria as a replacement diagnostic test for ovarian endometriosis. The results are detailed further in Table 2, including confidence intervals. The authors note significant heterogeneity between papers for most of the results. This was assessed through visual examination of forest plots and co-variate testing when more than 10 studies were available for a specific diagnostic test. In these cases, the authors were unable to identify the cause of heterogeneity.

Superficial Peritoneal Endometriosis

Reid et. al evaluated 189 women in a multicenter prospective diagnostic accuracy study [5]. Each woman suffered from chronic pelvic pain, underwent TVUS evaluation, and laparoscopic confirmation for endometriosis. The study used a specific TVUS technique to look for "soft-markers" such as ovarian immobility, Pouch of Douglas obliteration, and site-specific tenderness, then correlated the results with findings from laparoscopy to assess for diagnostic capabilities. For right ovary immobility, sensitivity and specificity for ipsilateral pelvic sidewall superficial endometriosis was 7.0% and 94% respectively. For left ovary immobility, sensitivity and specificity was 16% and 87% respectively. Confidence intervals were not provided. Additionally, site-specific tenderness to the left adnexa in the absence of ovarian immobility, Pouch of Douglas obliteration, and DIE was shown to be significantly correlated with left pelvic sidewall superficial endometriosis (p=0.024), although the sensitivity and specificity values were not provided and only 112 women met the criteria for this analysis.

Chowdary et. al conducted a retrospective diagnostic accuracy study to look specifically at pre-surgical factors that could be correlated with superficial endometriosis, including symptoms and TVUS characteristics [18]. Fifty-three women were identified as eligible for analysis in that they were receiving surgical evaluation of chronic pelvic pain or endometriosis, received TVUS as part of their preoperative work-up, and were not found to have DIE, ovarian endometriosis, or adenomyosis. One sonographer performed all the ultrasounds and was called "an experienced sonologist who has specialised in endometriosis" by the authors. Seventy-nine percent (42/53) of patients were found to have laparoscopic findings that matched TVUS findings (95% CI 68–90%, P<0.0001). Uterosacral ligament thickening on TVUS was found to

have a sensitivity and specificity of 0.62 and 0.73 respectively. Overall sensitivity and specificity values for any positive findings on TVUS were not provided.

Table 2. Sensitivity and specificity results from the included papers.

Study	Locations Assessed	Statistical Findings	Conclusions
Guerriero et. al, 2018. Transvaginal ultrasound vs magnetic resonance imaging for diagnosing deep infiltrating endometriosis: systematic review and meta-analysis.	Deeply infiltrating, specifically the rectosigmoid, rectovaginal septum, and uterosacral ligaments	Rectosigmoid: - Sensitivity: 0.85 (95% CI, 0.68–0.94) - Specificity: 0.96 (95% CI, 0.85–0.99) - LR+: 20.4 (95% CI, 4.7–88.5) - LR-: 0.16 (95% CI, 0.07–0.38) Rectovaginal septum: - Sensitivity: 0.59 (95% CI, 0.26–0.86) - Specificity: 0.97 (95% CI, 0.94–0.99) - LR+: 23.5 (95% CI, 9.1–60.5) - LR-: 0.42 (95% CI, 0.18–0.97) Uterosacral ligaments: - Sensitivity: 0.67 (95% CI, 0.55–0.77) - Specificity: 0.86 (95% CI, 0.73–0.93) - LR+: 4.8 (95% CI, 2.6–9.0) - LR-: 0.38 (95% CI, 0.29–0.50)	TVUS is useful as a first line tool for evaluating suspected deeply infiltrating endometriosis
Nisenblat et. al, 2016: Imaging modalities for the non-invasive diagnosis of endometriosis.	Deeply infiltrating and ovarian	Deeply infiltrating - Sensitivity: 0.79 (95% CI 0.69, 0.89) - Specificity 0.94 (95% CI 0.88, 1.00) Ovarian - Sensitivity: 0.93 (95% CI 0.87, 0.99) - Specificity: 0.96 (95% CI 0.92, 0.99)	TVUS is a useful first line tool for evaluating suspected endometriosis. A positive result at deeply infiltrating or ovarian sites is specific enough to rule in endometriosis.
Reid et. al, 2019. The association between ultrasound-based “soft markers” and endometriosis type/location: A prospective observational study.	Superficial peritoneal	Right ovary immobility - Sensitivity: 0.07 - Specificity: 0.94 - Likelihood ratios and confidence intervals not provided Left ovary immobility - Sensitivity: 0.16 - Specificity: 0.87 - Likelihood ratios and confidence intervals not provided Site-specific tenderness - Sensitivity, specificity, and likelihood values not provided	Certain soft-markers with TVUS can be a useful indicator in distinguishing and diagnosing superficial endometriosis from other locations.
Chowdary et. al, 2018. Multicentre retrospective study to assess diagnostic accuracy of ultrasound for superficial endometriosis- Are we any closer?	Superficial peritoneal	TVUS accuracy - 79% (42/53), 95% CI 68–90% Uterosacral ligament thickening - Sensitivity: 0.62 - Specificity: 0.73 - Unclear significance	It is possible to detect superficial endometriosis with considerable accuracy using TVUS with an experienced sonographer

Discussion

The primary objective of this narrative review is to analyze the diagnostic accuracy of TVUS compared to the traditional laparoscopic technique in diagnosing endometriosis at deeply infiltrating, ovarian, and superficial peritoneal sites. While the specificity of TVUS is high

enough to make it a valuable “rule-in” tool for evaluating deeply infiltrating and ovarian endometriosis, it lacks the sensitivity necessary to replace laparoscopy as a definitive diagnostic tool for these locations. Guerriero et. al concluded that TVUS performed well enough to be considered a first-line tool for evaluating a woman for DIE [17]. Nisenblat et. al concluded that TVUS meets criteria to be a useful tool to “rule-in” DIE and ovarian endometriosis, in that a positive TVUS from a well-trained sonographer can reliably diagnose endometriosis in those locations and, thus, should be considered a first line tool for evaluating women with suspected endometriosis [8]. For superficial peritoneal endometriosis, the data indicate that TVUS has potential to be a useful tool in assessing a woman with endometriosis, but Reid et. al and Chowdary et. al both concluded that more research is needed to be convincing [5,18].

While the generally low sensitivity values prohibit TVUS from being used as a replacement for laparoscopic diagnosis, the specificity values are impressively high across the board. Altogether, the research shows diagnostic utility in a positive TVUS, in that a patient can be diagnosed with endometriosis with reasonable certainty if they have a positive TVUS. However, a negative TVUS does not have the same utility. If a woman has a negative TVUS, the data here suggest further investigation is warranted before a provider can rule out endometriosis with reasonable certainty. This finding holds true for ovarian and deeply infiltrating sites. Despite only one of the reviews evaluating ovarian sites, the quality and completeness of the review is high enough to consider the findings reliable. The data is less convincing for superficial peritoneal sites given the lack of systematic reviews and overall limited data, but the foundation has been laid for future research at this location.

The quality of data available remains a major limitation of this narrative review. There are a limited number of studies evaluating the accuracy of TVUS in endometriosis diagnosis at deeply infiltrating and ovarian sites, and there are far fewer that analyze superficial peritoneal sites. As such, the quality of data available is stronger for deeply infiltrating and ovarian sites than superficial peritoneal sites. Of the studies that are available, they are limited by small sample sizes and poor methodological quality. This includes the diagnostic accuracy studies from Reid et. al and Chowdary et. al [5,18]. The challenge of small sample sizes can be partially alleviated with systematic reviews that include meta-analysis, although this produces the limitation of data heterogeneity, as seen in Nisenblat et. al and Guerriero et. al. Additionally, the

nature of the research question makes it difficult to include healthy controls, as it would be unethical to perform surgery on an otherwise healthy subject.

The inclusion of high-quality systematic reviews with extensive statistical analysis is the major strength of this narrative review. Nisenblat et. al in particular was impressively done, with data from over 4800 participants and methods that resulted in a low risk of bias [8]. Guerriero et. al included over 400 participants and was shown to have an unclear risk of bias, but included an extensive and very strong meta-analysis [17]. Strengths of this review are otherwise limited due to the reasons stated above.

The results of this narrative review reveal many opportunities for future research. In regards to ovarian and deeply infiltrating endometriosis, it is reasonable to conclude that TVUS is a useful tool in evaluating endometriosis in these locations when used by an experienced sonographer. Research evaluating the diagnostic accuracy of TVUS in the hands of a sonographer that does not specialize in endometriosis would serve to improve the usefulness of the tool in a setting outside of a tertiary gynecologic referral center. One study evaluating the learning curve for sonography students found that a two week course in endometriosis markers can improve a sonographer's accuracy to above 90% for most DIE locations [19]. This represents another opportunity for future research, as the validation of a sonography curriculum for endometriosis can greatly increase the standardization and access of endometriosis trained sonographers. In regards to superficial peritoneal endometriosis, larger studies evaluating TVUS as a tool for diagnosis are greatly needed. Future research opportunities should include larger studies specifically evaluating this location, inclusion of this location in systematic reviews and meta-analyses, and validation of positive TVUS markers for this location.

Conclusions

Endometriosis is a complicated disease process that results in ectopic implantation of endometrial tissue. Most implants can be classified as deeply-infiltrating, ovarian, or superficial peritoneal based on their locations within the pelvis. Women who have endometriosis can suffer from physical and non-physical sequelae, including dysmenorrhea, dyspareunia, noncyclic pelvic pain, dyschezia, dysuria, depression, anxiety, lost income, and mistrust of healthcare professionals. The average time to diagnosis is 8-12 years, a delay that is in part due to the requirement of laparoscopy for diagnosis.

This narrative review sought to understand the current research available for evaluating TVUS as a diagnostic tool for deeply infiltrating, ovarian, and superficial peritoneal endometriosis. The results reveal a high specificity and limited sensitivity for TVUS at DIE and ovarian sites. More research is needed to further validate and standardize evaluation at these sites, but the data here is strong enough to consider TVUS a useful first-line tool in the evaluation of endometriosis at deeply infiltrating and ovarian sites. In fact, these results suggest a positive TVUS can reliably establish the diagnosis of endometriosis at ovarian and deeply infiltrating sites. However, a negative TVUS cannot rule out the diagnosis of endometriosis, and a provider should pursue further testing and maintain a high degree of suspicion for the disease. The data available for superficial peritoneal sites is currently too limited to draw conclusions and significant more research is needed.

Overall, this review reveals that TVUS is a useful, noninvasive, low-cost tool in evaluating a woman for endometriosis and has the potential to reduce the time to diagnosis and treatment, thereby greatly reducing the burden of disease for a woman. Providers should be confident and empowered to use TVUS as a first line in evaluating a woman with a clinical picture consistent with endometriosis. This tool can be an important component of improving a patient-provider relationship, in that this is a relatively easy, low-cost way for a provider to try and reach some answers for a patient. However, the consequences of the poor sensitivity values should be discussed in detail with patients. Patients and providers should be aware that a negative TVUS does not rule out endometriosis, and providers will need to maintain a high degree of suspicion and pursue further testing if this is the result.

Appendix 1: Table of excluded studies

Study [Year]	Reason for Exclusion
Aloisi [2018] [20]	Does not evaluate TVUS (only evaluates laparoscopic narrow band imaging)
Anaf [2009] [21]	Does not evaluate TVUS (only evaluates barium enema)
Audebert [2015] [22]	Not related to primary outcome
Barra [2018] [23]	Not related to primary outcome
Borsellino [1993] [24]	Published prior to 2009
Casasayas-Carles [2014] [25]	Not related to primary outcome
Daraï [2014] [26]	Not related to primary outcome
Deffieux [2004] [27]	Published prior to 2009
Fancellu [2013] [28]	Case report and not related to primary outcome
Fastrez [2017] [29]	Does not evaluate TVUS (only evaluates specific type of PET-CT scan)
Fernandez [2003] [30]	Published prior to 2009
Gabriel [2011] [31]	Not related to primary outcome
Gonçalves [2016] [32]	Not related to primary outcome
Guerriero [2015] [33]	More recent study published from the same lead author
Guerriero [2016] [34]	More recent study published from the same lead author
Hernández [2005] [35]	Published prior to 2009
Hudelist [2011] [36]	Results are specific to bowel endometriosis and are not suitable for comparison with diagnosing DIE as a whole
Jaramillo-Cardoso [2018] [37]	Not a systematic review and does not evaluate superficial endometriosis (only evaluates abdominal-wall endometriosis)
Keckstein [2000] [38]	Published prior to 2009
Khan [2018] [39]	Does not evaluate TVUS (only evaluates MRI)
Kiesel [2019] [3]	Not a systematic review and does not evaluate superficial endometriosis
Kruse [2012] [40]	Not a systematic review and does not evaluate superficial endometriosis
Leone [2016] [41]	Only evaluated women during active pregnancy
Levy [2013] [42]	Not related to primary outcome
Ma [2019] [43]	Not related to primary outcome
Maignien [2017] [44]	Not related to primary outcome

McCausland [1996] [45]	Published prior to 2009
McCausland [1998] [46]	Published prior to 2009
Moawad [2013] [47]	Not a systematic review and does not evaluate superficial endometriosis
Moore [2002] [48]	Published prior to 2009
Muzii [2016] [49]	Not related to primary outcome
Nisenblat [2016] [50]	Only evaluated TVUS diagnostic potential when combined with other tests; derivative of included systematic review (Nisenblat, 2016)
Noventa [2015] [51]	Included diagnostic data from non-TVUS techniques
O'Callaghan [2006] [52]	Published prior to 2009
Parazzini [2018] [53]	Not related to primary outcome
Pickhardt [2007] [54]	Published prior to 2009
Piessens [2019] [55]	Does not include laparoscopy and histology as reference value
Ribeiro [2006] [56]	Published prior to 2009
Rimondi [2018] [57]	Not related to primary outcome
Salvat [2001] [58]	Published prior to 2009
Scardapane [2013] [59]	Does not evaluate TVUS (MRI-only review)
Shoji [2016] [60]	Case report, not related to primary outcome
Silveira [2018] [61]	Does not evaluate TVUS; animal study
Streuli [2017] [62]	Not related to primary outcome
Valentini [2014] [63]	Does not evaluate TVUS (only evaluates MRI)
Wozniak [2015] [64]	Not related to primary outcome
Zhang [2018] [65]	Case report and not related to primary outcome

Appendix 2: AMSTAR 2 Risk of Bias tool for systematic reviews

AMSTAR 2 Criteria	**Nisenblat et. al, 2016**	**Guerriero et. al, 2018**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No; they did provide a list of reasons why studies were excluded, but not a list of the specific studies	No; they did provide a list of reasons why studies were excluded, but not a list of the specific studies
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes, QUADAS-2 tool	Yes, QUADAS-2 tool
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes, within the QUADAS-2 tool	Yes, within the QUADAS-2 tool
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes
13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Yes	Yes

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No, there is no explicit statement regarding sources of funding or conflicts of interest

Appendix 3: QUADAS-2 tool for primary literature

QUADAS-2 Criteria	**Chowdary et. al**	**Reid et. al**
Review Question	Do ultrasound findings of superficial endometriosis correlate with laparoscopic findings?	Are ultrasound 'soft markers' associated with endometriosis type and location based on laparoscopic findings?
Index Test	Transvaginal ultrasound	Transvaginal ultrasound
Reference Test	Laparoscopy with histologic sampling	Laparoscopy with histologic sampling
Patient Selection: Risk of Bias 1. Was a consecutive or random sample of patients enrolled? 2. Was a case-control design avoided? 3. Did the study avoid inappropriate exclusions? 4. Could the selection of patients have introduced bias?	1. Yes, consecutive 2. Yes, all cases 3. Yes, only excluded incomplete patients 4. LOW RISK	1. Yes, consecutive 2. Yes, all cases 3. Yes, only excluded women who did not receive laparoscopy 4. LOW RISK
Patient Selection: Applicability 1. Is there concern that the patients do not match the review question?	1. LOW RISK	1. LOW RISK
Index Test: Risk of Bias 1. Were the index test results interpreted without knowledge of the results of the reference standard? 2. If a threshold was used, was it pre-specified? 3. Could the conduct or interpretation of the index test have introduced bias?	1. Yes, performed prior 2. Yes, predefined and only one technician 3. LOW RISK	1. Yes, performed prior 2. Yes, positive test was pre-defined and given to technicians 3. LOW RISK
Index Test: Applicability 1. Is there concern that the index test, its conduct, or interpretation differ from the review question?	1. LOW RISK	1. LOW RISK
Reference Standard: Risk of Bias 1. Is the reference standard likely to correctly classify the target condition? 2. Were the reference standard results interpreted without knowledge of the results of the index test? 3. Could the reference standard, its conduct, or its interpretation have introduced bias?	1. Yes, gold standard 2. Yes, no knowledge of index test results 3. LOW RISK	1. Yes, gold standard 2. Unclear, does not state if surgeons knew TVUS results 3. UNCLEAR RISK
Reference Standard: Applicability 1. Is there concern that the target condition as defined by the reference standard does not match the review question?	1. LOW RISK	1. LOW RISK
Flow and Timing: Risk of Bias 1. Was there an appropriate interval between index test(s) and reference standard? 2. Did all patients receive a reference standard? 3. Did patients receive the same reference standard? 4. Were all patients included in the analysis? 5. Could the patient flow have introduced bias?	1. Yes, reference test after index 2. Yes 3. Yes 4. Yes, 30 histories incomplete 5. LOW RISK	1. Yes, reference test after index test 2. Yes 3. Yes 4. Yes, 31 excluded for not receiving reference 5. LOW RISK

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