Literature review: deep endometriosis diagnostic and treatment challenges

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Abstract

Background and aim. Deep endometriosis (DE) is defined as endometriotic lesions that extend more than 5 mm below the surface of the peritoneum. Women of reproductive age with this disease experience pain, infertility, and a consequent decline in quality of life. Deep endometriosis' exact mechanics and pathophysiology remain poorly known, which makes diagnosis and treatment challenging.

Materials and Methods. We searched PubMed and Google Scholar databases to compare the diagnostic value of non-invasive procedures like transvaginal ultrasound and magnetic resonance imaging with diagnostic laparoscopy with tissue biopsy. We also used the same databases to research the best deep endometriosis treatment strategy.

Results. The quality of non-invasive diagnosis highly depends on the deep endometriosis location. #Enzian classification is a valuable tool in improving the sensitivity and specificity of TVUS. The treatment options differ throughout different guidelines; however, they all agree that treatment should be individualized depending on the patient's age and complaints.

Conclusion. Non-invasive diagnostic techniques can safely replace diagnostic laparoscopy; however, their site-specificity and the need for a trained professional should be kept in mind. Conservative therapy should be the first line for pain management, and assisted reproductive techniques should be used for infertility treatment. Surgery should only be considered when both of these options are exhausted.

Keywords: deep endometriosis, non-surgical diagnosis, treatment, pain, infertility.

1. Introduction

Rokitansky was the first to describe deep endometriosis disease. Later, T. Cullen described it as adenomyosis of the round ligament. As new discoveries were made over time, the definitions evolved. DE, formerly known as deep infiltrative endometriosis, is now most commonly defined as endometriotic lesions that extend more than 5 mm below the surface of the peritoneum (1). Deep endometriosis' pathophysiology is not entirely understood, just like it is for the other types of endometriosis (2). DE symptoms vary based on the location and do not correlate with the severity of the condition. It tends to affect rectovaginal fascia, rectum, uterosacral ligaments, small bowel, omentum, urinary tract, and vagina (3). Estimating the prevalence of DE is challenging because a definitive diagnosis can only be acquired after diagnostic laparoscopy with tissue biopsy. DE affects fertile-age women and results in pain, infertility, and a lower quality of life, continuing to be a significant medical issue (4). The Enzian classification was the main classification used for deep endometriosis; however, it does not evaluate peritoneal and ovarian endometriosis and adhesions. Therefore, the #Enzian classification was developed to estimate all forms of endometriosis, enabling assessment of the full scope of the disease (5,6). This review will discuss some diagnostic and therapeutic challenges arising from the lack of knowledge about deep endometriosis.

2. Materials and methods

To evaluate whether non-invasive procedures like transvaginal ultrasound or magnetic resonance imaging can take the role of diagnostic laparoscopy with tissue biopsy, we performed a search using PubMed and Google Scholar databases. In addition, the same databases were used to search for the best treatment strategy for DE.

3. Discussion

3.1. Diagnosis

Transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI)

Discussing diagnosis, the primary question is which diagnostic method is the most accurate and whether invasive diagnostic laparoscopy can be avoided. Clinical examination should proceed as with other endometriosis forms, focusing on symptoms such as dysmenorrhea, dyspareunia, dyschezia, dysuria, chronic pelvic pain, and infertility, also evaluating previous medical history along with the family history of possible endometriosis. However, endometriosis may be asymptomatic, making a diagnosis based solely on anamnesis and symptoms insufficient (7–9). Therefore, the next step should be a clinical examination, which includes checking the posterior vaginal fornix with a speculum for dark nodules and retraction, as well as performing a digital exam to assess the uterus' mobility and consistency and check for any potential bladder, uterosacral ligament, rectovaginal fascia and the pouch of Douglas invasions. Finally, digital examination per rectum can reveal rectal involvement. However, it can be painful, and the authors disagree on the sensitivity and specificity of clinical examination. (7,10).

Usually, TVUS does not require any preparation; however, some studies have indicated that bowel preparation can improve TVUS results because it clears gas and feces from the rectosigmoid colon, which enhances the image of the pelvic cavity and removes artifacts (11,12). Another method for improving imaging of the vagina and rectovaginal septum during TVUS is to add some couplant to the

probe condom since the air space between the vagina and the probe can create artifacts (13). To assess the anterior compartment and uterus effectively, patients should empty the bladder and drink a glass of water just before the procedure (11). The International Deep Endometriosis Analysis (IDEA) group proposed a four-step TVUS assessment algorithm. A routine examination of the uterus and adnexa for adenomyosis and endometriomas is the first step. In the second step, "soft markers" are evaluated. The third step evaluates Dougla's pouch based on the 'sliding-sign'. The last step is the assessment of deep endometriosis nodules in anterior and posterior compartments. Instead of random inspection, this technique enables sonographers to do so in a systematic manner for greater accuracy. (10). TVUS sensitivity and specificity were evaluated by S. Yin et al. based on the site of deep endometriosis. When diagnosing uterosacral ligament endometriosis, TVUS had the maximum sensitivity (96,75%). Sensitivity and specificity of 73,68% and 94,33%, respectively, for rectovaginal septum, also suggest significant diagnostic value. The broad ligament's deep endometriosis had the lowest detection sensitivity (10%). However, this site's specificity was 100%. Intestinal endometriosis had the highest correlation between TVUS and surgical findings; TVUS sensitivity and specificity were 94,94 % and 94,96 %, respectively. TVUS sensitivity of other deep endometriosis sites ranges from 73,68 % to 50 %, and specificity ranges from 100 % to 94,33 %. We can conclude from this study that while the diagnostic value of ultrasonography depends on the site, DE of the uterosacral ligaments, intestine, and rectovaginal septum has the highest diagnostic value (13). Using the #Enzian classification, E. Montanari et al. carried

out a prospective multicenter study on the diagnostic accuracy of sonography for the non-invasive diagnosis of ovarian and deep endometriosis. Researchers concluded that endometriotic lesions could be accurately and non-invasively detected with TVUS because there was an 86% to 99% correlation between TVUS and surgical findings, depending on the #Enzian compartments under examination. (14). The final point we want to emphasize is its low cost and emphasis on rectovaginal endometriosis and uterosacral ligaments; yet, it is skill- and experience-dependent. (11,13).

Deep endometriosis can be detected by magnetic resonance imaging (MRI) as "implants or tissue masses that present as hypointense areas and/or hyperintense foci on T1- or T2-weighted images in the following locations: the torus uterinus, uterosacral ligaments, vagina, rectovaginal septum, rectosigmoid, pouch of Douglas, parametrium, bladder, and round ligaments" (7). MRI is usually performed as a second-line investigation which should be performed using ether1, 5-T, or 3-T magnets. Preparation for MRI requires 4 hours of fasting before the examination to avoid vomiting. The same method described for TVUS, bladder preparation may be employed because the bladder should be fairly filled. However, there is no consensus among authors on whether bowel preparation improves accuracy (7,15,16).

In a meta-analysis, V. Nisenblat et al. compared TVUS and MRI to diagnostic laparoscopy. TVUS's sensitivity and specificity for detecting deep endometriosis were 79 % and 94 %, respectively, which approached the criteria for SpPin triage test. The sensitivity and specificity of the MRI were 94 % and 77 %, respectively, reaching the standards for a replacement test and a SnNout triage test (table 1).

Deep endometriosis	Sensitivity	Specificity	SpPin triage test	SnNout triage test	Replacement
TVUS	79%	94%	Approached the criteria	Did not qualify	Did not qualify
MRI	94%	77%	Did not qualify	Approached the criteria	Approached the criteria

Table 1. The sensitivity and specificity of TVUS and MRI diagnosing deep endometriosis. TVUS approached the criteria for SpPin triage test but did not qualify for SnNout triage test and replacement test. MRI approached the criteria for both SnNout triage and replacement tests but did not qualify for SpPing triage test (N).

According to the available information, TVUS has a higher diagnostic value as a non-invasive technology than MRI and can be utilized for preoperative planning more effectively (17). P. V. Foti et al. disagree with this study and contend that the best method for preoperative staging of endometriosis is magnetic resonance imaging. Yet to reach this result, this study also considered ovarian and peritoneal endometriosis. It also gives sensitivity and specificity depending on deep endometriosis locations (18). As V. Nisenblat et al. meta-analysis does not evaluate MRI sensitivity and specificity in relation to particular sites, it is difficult to compare these two investigations fairly. S. Guerriero et al. systematic review and meta-analysis assessed the sensitivity and specificity of TVUS and MRI of specific sites such as the rectosigmoid, rectovaginal septum, and uterosacral ligaments. TVUS and MRI performed similarly in terms of diagnostic power, with the maximum sensitivity only reaching 70 % and specificities for all sites ranging from 86 % to 97 %. The least sensitive diagnostic methods for detecting endometriosis of the rectovaginal septum were TVUS and MRI, with sensitivity values of 59 % and 66 %, respectively. Both techniques showed the highest and equal specificity for rectosigmoid endometriosis at 85 % (19).

Having discussed TVUS and MRI, we believe that TVUS can replace diagnostic laparoscopy and should be prioritized, considering the cost. According to patient complaints, MRI may be employed as a second-line diagnostic method for sites with reduced TVUS sensitivity. Yet, because studies have produced varying outcomes and were conducted in various ways, we are unable to determine which diagnostic technique is better.

3.2. Treatment

3.2.1. Pharmaceutical therapy

Medical therapy should be the first choice in treating deep endometriosis as the disease can affect the whole bowel, and the excision of deep lesions may lead to major and minor complications (20,21). Progestins are recommended as the first-line treatment for women with endometriosis in all six national and two international guidelines that D.R. Kalaitzopoulos et al. reviewed (21). The primary choice for progestins should be Dienogest as it has shown significant pain relief; however, it has practically no effect on reducing the size of endometriotic implants (21–23). Combined oral contraceptive pills should be the first choice for empirical treatment for patients who do not wish to conceive (21)). NSAIDs can also be used as first-line treatment for pain management; however, long-term

use can cause side effects, and a Cochrane review showed no effect compared to placebo (21,24). Gonadotropin-releasing hormone agonists/antagonists and aromatase inhibitors are the second-line treatments. They should only be used if the first-line treatment fails as they have more side effects, and aromatase inhibitors should not be used as monotherapy but in combination with first- or second-line drugs (21). Conservative treatment has shown to be helpful in stopping the lesions' growth and inducing their regression. However, when a medication is stopped, the problems frequently return (21,25).

3.2.2. Pain and infertility

As previously stated, medical therapy should be the first line of treatment for women whose primary complaint is pain. The patient should continue medical therapy if the disease is stable after the follow-up. However, surgery should be considered if pharmaceutical treatment fails and the pain persists or worsens, or pain during the time of endometriosis diagnosis was seven or more according to the visual analog scale (VAS). If a woman experiences pain and infertility, the Anti-Mullerian hormone (AMH) and the patient's age should be evaluated. The initial option should be surgery followed by in vitro fertilization (IVF) if AMH is normal and the age is 30 years or less. Surgery should be performed after gamete cryopreservation if AMH is low and the patient is older than 30. (20). If medical therapy fails in pain relief or the pain score according to VAS is seven or more, hysterectomy with or without bilateral salpingo-oophorectomy can be suggested to women who have completed their families (20,21).

According to R. M Kho et al. comparison of the major society guidelines, assisted reproductive techniques should be the first choice if fertility is the main symptom. Surgery is advised if IVF fails twice (20).

The excision of deep endometriosis before assisted reproductive techniques has been shown to increase fertility in endometriosis stages I and II, despite the major guidelines suggesting that surgery should only be performed if IVF fails twice. This is because surgery aims to restore normal pelvic anatomy and remove macroscopic implants (26,27). According to a comprehensive review and meta-analysis by G. Casals et al., surgery improves the success of IVF. However, predicting the precise effect of eliminating DE is challenging because it frequently coexists with ovarian endometriosis and adenomyosis. The authors also state the lack of randomized controlled trials on this topic (28).

4. Conclusion

DE diagnosis should take into account symptoms, medical background, digital assessment, and imaging. TVUS has a high diagnostic value for DE of the uterosacral ligaments, intestine, and vaginal rectal septum but largely depends on the location of endometriosis and the doctor's experience. The use of #Enzian classification improves the accuracy of TVUS. Sonography is regarded as the primary diagnostic method, with MRI being employed for locations where TVUS is less sensitive. This means diagnostic laparoscopy with tissue biopsy should only be utilized as a last-resort approach when TVUS and MRI results are ambiguous, and symptoms worsen. The first-line treatment for DE should be pharmaceutical therapy, preferably starting with Dienogest. However, the main problem with medical therapy is that it has little effect on already existing lesions, and symptoms tend to recur when therapy is terminated. Assisted reproductive techniques should be considered for patients whose primary symptom is infertility. Surgery should only be considered when medical treatment or IVF fails.

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