DSOG Guideline Bulletin: Diagnostic approach for patients with endometriosis

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ABSTRACT

The aim of this guideline was to update an existing guideline from 2012. An update was evident due to the scientific progress and political focus on endometriosis in recent years. Based on recent evidence, we aimed to provide clinical recommendations for training and use of ultrasound, magnetic resonance imaging (MRI), computed tomography, and diagnostic scoring systems, as well as diagnostic considerations when evaluating patients suspected for endometriosis. Current literature was searched for consensus and discrepancies. A total of eight research questions were formulated to review different aspects, when diagnosing endometriosis. The level of evidence was graded according to the Oxford Centre for Evidence-based Medicine Levels of Evidence and up- or downgraded depending on the study quality. According to the current literature, no diagnostic imaging tool can replace histologic verification of endometriosis except ultrasound when diagnosing lesions in the abdominal wall. Skills for diagnosing endometriosis in the posterior compartment with transvaginal ultrasound (TVUS) can be achieved within 50-60 scans. TVUS seems equivalent to MRI when endometriosis is suspected in the vagina, the sacrouterine ligaments, the rectovaginal fascia, and the rectosigmoid. Additionally, ultrasound has a high sensitivity for diagnosing endometriotic lesions in the abdominal wall, while MRI seems superior for deep infiltrating endometriosis (DIE) in the bladder, the ureter, the lumbosacral plexus, lungs and oral segment of the colon starting from the rectosigmoid. No biomarkers are currently recommended for diagnosing endometriosis. When considering bowel involvement, 60-96% of DIE in the colon is localized in the rectum with decreasing rates in the oral segments with a prevalence of affected appendix of 2.6-4.1%. Measuring the distance from the anocutaneus transition to the nodule is feasible with TVUS. The most promising grading systems for endometriosis are the EFI, #ENZIAN and AAGL scoring systems. The level of evidence across studies ranged from 1b to 5.

Keywords: Endometriosis; Diagnostic imaging; Endometrioma; Pelvic disease

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INTRODUCTION

The last national guideline for diagnosing endometriosis is from 2012. Several international conferences have been held since, focusing on diagnosis of endometriosis. In Denmark, political concerns have been raised regarding the diagnostic delay of endometriosis. In 2016, The International Deep Endometriosis Analysis (IDEA) Group published a systematic 4-step protocol for diagnostic evaluation of endometriotic lesions with transvaginal ultrasound (TVUS) [1]. Thus, an updated guideline was needed to evaluate the recent advances in diagnostic imaging of endometriosis. As the usefulness of TVUS for endometriomas are previously mentioned in recent national guidelines from 2017 and 2020, this updated guideline focused on different aspects diagnosing endometriosis [2–4].

In this updated guideline, we aimed to clarify the advantages and limitations of diagnostic imaging of deep infiltrating endometriosis (DIE) as well as the diagnostic approach for endometriosis in the subcutis, abdominal wall, lungs, and sacral nerves. Recent advances in diagnostic biomarkers were reviewed as well as several endometriosis scoring systems for better surgical preparation. Finally, the performance of TVUS depends on the experience and skills of the clinician. Therefore, research focusing on the learning curve of the IDEA protocol was also reviewed.

OBJECTIVES

In total, eight PICO/PIRO questions were developed for this guideline:

1. Can diagnostic imaging (ultrasound and MRI) replace laparoscopy with biopsy in evaluating women with cyclical pain?
2. Is TVUS or MRI superior for diagnosing DIE in women being suspected for endometriosis?
3. Which imaging method is best for diagnosing endometriosis in the abdominal wall?
4. Which imaging method is best for diagnosing endometriosis in the lungs?
5. How is endometriosis diagnosed in the lumbosacral nerves?
6. Is it possible to diagnose endometriosis with a blood test?
7. What are the benefits and limitations of current scoring systems for endometriosis?
8. How many supervised TVUS must be performed to gain competence in endometriosis diagnostics, and how should a training program be designed to obtain the best prerequisites?

METHODS

PubMed was searched for included articles and a search string was developed for each research question. The search was performed between December 2021 and February 2022. For studies investigating imaging modalities for diagnosing deep infiltrating endometriosis, laparoscopic or histological confirmation was used as the reference value. Covidence.org was used as the primary screening tool. The Oxford Centre for Evidence-based Medicine, Levels of Evidence grading system, was used to grade the study quality. The guideline was presented and approved on the “Danish Society of Obstetricians and Gynaecologists” annual meeting the 16th of September 2022.

RESULTS

Can diagnostic imaging (ultrasound and MRI) replace laparoscopy with biopsy in the evaluation of women with cyclical pain?

A Cochrane review (2016) concluded that TVUS was not a qualified replacement for surgery in diagnosing pelvic endometriosis. However, TVUS demonstrated a high sensitivity (93%) and specificity (96%) in diagnosing endometriomas, as

well as diagnosing DIE in the rectovaginal fascia, pouch of Douglas, sacrouterine ligaments, and rectosigmoid (specificity: 94%, sensitivity:79%) [5].

Histological verification of endometriosis

Histological verification of endometriosis remains a topic of debate, as macroscopic elements are not consistently analysed. In 2004, a review of four studies with 433 biopsies found that macroscopic findings were consistent with positive histology. However, the histological verification of endometriosis varied from 18% to 77% within the included studies [6]. The European Society of Human Reproduction and Embryology (ESHRE) recommends in their 2022 guideline that endometriosis lesions should be identified with laparoscopy and confirmed histologically, except ultrasound for lesions located in the abdominal wall. Additionally, the ESHRE guideline recommends that laparoscopy should be considered in the event of negative diagnostic imaging and absence of medical treatment effect [7].

Is TVUS or MRI best for diagnosing deep infiltrating endometriosis in women being evaluated for endometriosis?

For diagnosing DIE in the bladder, TVUS demonstrated a sensitivity of 55% and a specificity of 99%. In comparison, MRI demonstrated a sensitivity of 50%-70% and a specificity of 100% [8]. For DIE of the ureter, TVUS demonstrated a sensitivity range of 10-100% and a specificity range of 95-100%, while MRI showed a sensitivity range of 56-100% and a specificity of 100% [9]. For diagnosing DIE in the bladder and ureter, TVUS must be supplemented with MRI.

For diagnosing DIE of the rectovaginal septum (RVS) and the uterosacral ligaments (USL), both TVUS and MRI perform equally (RVS TVUS/MRI: Sensitivity 59/66%, Specificity 97/97%; USL TVUS/MRI: Sensitivity 67/70%, Specificity 86/93%) [10].

For diagnosing DIE in the rectosigmoid, TVUS and MRI perform equally [10–13]. However, ultrasound is not recommended for diagnosing bowel DIE orally from the rectosigmoid, due to limited visualization. In the rectosigmoid, TVUS was considered superior to MRI for predicting the depth of bowel wall infiltration, and rectosigmoid stenosis can be assessed with water-based contrast.

It is feasible to measure the distance from the anocutaneous transition to the lower edge of a rectal nodule with TVUS, by combining distances from the vaginal probe's index finger and the probe to the nodules' lower edge on the ultrasound image [14].

Distribution of DIE in the bowel

Incidence rates of DIE in different bowel locations in women diagnosed with endometriosis are reported with 58.9-96.0% located in the rectum, 50.0-65.7% in the rectosigmoid, 8.8-62.5% in the sigmoid, and 2.5-4.1% in the appendix. DIE in more than three locations increase the risk of DIE in the appendix (OR 3.0, CI95% 2.2-4.1) [15–22].

Which imaging method is best for diagnosing endometriosis in the abdominal wall?

Endometriosis in the abdominal wall is rare, occurring in 0.03%-1% of patients with previous caesarean section. Meta-analysis and systematic review findings suggest ultrasound, CT, or MRI for diagnosis, but no modality has been established as superior [23]. Ultrasound is non-invasive, cost-effective, and highly sensitive. A study including 12 women with endometriosis demonstrated a sensitivity of 92% when ultrasound was used [24]. MRI is suitable for distinguishing between different tissue planes (subcutis/muscles) and may accurately determine the exact extent of lesions, including fascial or muscle involvement [25].

Which imaging method is best for diagnosing endometriosis in the lungs?

Thoracic endometriosis-syndrome is rare and currently only reported in case series. Symptoms include cyclic chest pain, dyspnoea and haemoptysis. 70-85% present with pneumothorax of which 80-92% are located on the right side [26,27]. The diagnosis verified with thoracoscopy, with only seven existing case studies (9 patients) comparing MRI with CT for diagnosing thoracic endometriosis syndrome. Compared to CT, MRI of DIE is more detailed and can differentiate endometriotic nodules from other pathologies [28–33].

How is endometriosis diagnosed in the lumbosacral nerves?

Endometriosis in the lumbosacral nerves is rare. The condition should be suspected in cases of cyclic pain or disturbances in areas innervated by the lumbosacral nerves; such as sciatic pain, drop foot, sensory disturbances, leg weakness. Symptoms located on the right side is most frequent and it is important to diagnose the condition early in order to prevent permanent nerve damage [34–36]. A neurological and radiological examination is necessary to exclude differential diagnoses [37]. MRI is considered the best diagnostic tool for detecting endometriosis in the lumbosacral nerves, with a sensitivity of 90% and specificity of 98% for diagnosing endometriosis in the sciatic nerve. MRI can be performed independently of the menstrual cycle [38].

Is it possible to diagnose endometriosis with a blood test?

Many biomarkers have been investigated. The most well-studied and recommended marker for diagnosing endometriosis is cancer antigen 125 (CA-125) [39,40]. CA-125 has a significantly higher sensitivity for diagnosing moderate and severe endometriosis, compared to mild endometriosis (63% vs. 24%) [41]. For the diagnosis of mild to moderate endometriosis the autoantibodies anti-SLP2, anti-TMOD3, anti-TPM3, and anti-PDIK1L have shown promising results [40]. However, none of the these investigated biomarkers, including CA-125, meet the criteria for a useful diagnostic test (sensitivity ≥0.94, specificity ≥0.79).

What are the benefits and limitations of current scoring systems for endometriosis?

The AFS/rASRM score has been used for decades, to map the extent of endometriosis [42,43]. The EFI score estimates the chance of spontaneous pregnancy after surgery and has been validated in several studies [44]. The ENZIAN score maps DIE, and the #ENZIAN score maps endometriosis in all areas including DIE detected later at surgery or by imaging. Both scores have been validated and are correlated to clinical outcomes [45,46]. The AAGL society has developed a validated score, estimating the severity of endometriosis at surgery. This score is superior to the ASRM score when estimating the complexity of surgery [47].

How many supervised TVUS must be performed to gain competence in diagnosing endometriosis and how should a training program be designed to obtain the best prerequisites?

Skills in diagnosing endometriotic lesions, were achieved with varying attempts, depending on the location of the lesion:

- Endometriomas with an error rate of 10-15% required 18-40 scans [48,49].
- DIE in the bladder with an error rate of 2.5-10% required 14-26 scans [48,50].
- DIE in the rectosigmoid with an error rate of 2.5–17.5% required 21–60 scans [48,50–53].
- Sliding sign with an error rate of 10–17.5% required 22–56 scans [48,51,53,54].
- DIE in the sacrouterine ligaments with an error rate of 2.5-10% required 27-58 scans [48,50].
- Endometriosis in the rectovaginal septum with an error rate of 2.5% required 14-43 scans [50].
- Endometriosis in the vagina with an error rate of 10% required 32 scans [48].

The best results were achieved within 50-60 scans if optimal prerequisites were present, including previous experience with TVUS, training, supervision and continuity at a tertiary center.

CONCLUSIONS

This guideline provides an overview of the diagnostic approach of patients with endometriosis and adds information on distribution of deep infiltrating endometriosis in the colon as well the expected learning curve for achieving relevant ultrasound skills. The ESHRE guideline together with this updated national guideline provides useful information for preventing diagnostic and treatment delay for patients with endometriosis. Two tables are listed below with the summary of evidence and clinical recommendations. A level of evidence-score of 1 is considered the highest level of evidence, and a recommendation strength of A is considered the highest recommendation.

TABLE OF SUMMARY OF EVIDENCE

Summary of evidence	Level of evidence
No imaging studies can entirely replace laparoscopy for the diagnosis of endometriosis except ultrasound for endometriosis in the abdominal wall. Comparison of studies is challenged due to great heterogeneity between the studies.	2b
Anterior compartment: Transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) have comparably low sensitivity for the diagnosis of deep infiltrating endometriosis (DIE) in the bladder and ureter. A cohort study finds MRI superior for detecting DIE in the bladder and ureter.	2b
Posterior compartment: The is no significant difference between TVUS and MRI for the diagnosis of DIE in the sacrouterine ligaments and the rectovaginal septum. A retrospective cohort study finds that objective examination and MRI have the highest sensitivity and specificity for the diagnosis of rectovaginal endometriosis.	2b/c
A prospective cohort study finds no difference between TVUS and MRI for the diagnosis of endometriosis in the vagina. A retrospective cohort study finds that MRI has the highest sensitivity, while TVUS has the highest sensitivity for vaginal endometriosis in another retrospective cohort study. The studies are small.	2c
Two meta-analyses and two cohort studies find no difference between TVUS and MRI for the diagnosis of DIE in the rectosigmoid.	2b
60-96% of DIE in the colon is localized to the rectum, and with decreasing frequency in the rectosigmoid, sigmoid, and coecum.	3b
The prevalence of endometriosis in the appendix is 2.6-4.1%.	3b
Endometriomas located on the right side of > 5 cm combined with DIE in the pelvis and ileocecal affection increase the likelihood of endometriosis in the appendix.	2b
Stenosis in the rectum/rectosigmoid can be assessed by MR colonography. If nodular infiltration in the intestinal lumen > 11 mm, stenosis of the rectum can be suspected	3b
The use of water-based contrast in the rectum during ultrasound examination may contribute when assessing stenosis in the colon.	3b
TVUS is a reproducible method for measuring the distance from the anocutaneous transition to the lower edge of an endometriotic nodule in the rectum.	1b
Ultrasound has high sensitivity in the diagnosis of endometriosis in the abdominal wall.	4

MRI can be used as a supplementary for preoperative assessment, as well as considering the involvement of fascia or musculature.	4
3D scanning requires specialized expertise and can be used in selected cases.	5
Compared to CT, MRI may contribute to differentiated diagnostics of endometriosis in the lung parenchyma, pleura, and diaphragm.	4
Endometriosis in the lumbosacral nerves is rare.	5
Cyclic pain corresponding to the lumbosacral plexus, especially on the right side, may indicates infiltration of endometriosis. Neurological examination and radiological examinations may benefit when considering differential diagnostics.	2a
Rapid diagnosis of endometriosis in the lumbosacral nerves is estimated to reduce the risk of permanent nerve damage.	2b
MRI scanning has a reported sensitivity of 90% and specificity of 98% for diagnosing endometriosis involving the sciatic nerve.	2a
MRI scanning is the preferred method for diagnosing endometriosis involving the nerves of the lumbosacral plexus.	2b
The literature on biomarkers for the diagnosis of endometriosis consists of studies with great heterogeneity and low quality. More clinical studies are needed to determine the potential of the individual biomarkers for diagnostic purposes.	3a
CA-125 has limited diagnostic value in patients with endometriosis. The combination with non-invasive tests is not yet known.	3a
AFS/rASRM, EFI, ECO, UBESS, and ENZIAN/#ENZIAN as well as AAGL Score uncover different aspects of endometriosis. AFS/rASRM, UBESS, ENZIAN/#ENZIAN, and AAGL have mainly describe anatomical extent or severity of endometriosis. EFI is developed for assessing the chance of achieving pregnancy after surgery. The Enzian score describes the DIE. As #Enzian and AAGL are recently developed, further publications are awaited regarding their usefulness. The advantage of #Enzian is expected to be able to uncover the entire symptomatology of endometriosis.	1a
When training at a tertiary center, physicians familiar with ultrasound diagnostics can probably achieve the ability to diagnose nodules in the rectum/rectosigmoid, as well as sliding sign, within 50-60 scans.	2b

TABLE OF CLINICAL RECOMMENDATIONS

Recommendations		**Strength**
Transvaginal ultrasound (TVUS) should always supplement the medical history and be included as part of the objective examination when endometriosis is		B

suspected.		
Ultrasound may be used to diagnose endometriosis in the abdominal wall.		D
Laparoscopy can be considered for diagnosing and treating suspected endometriosis in the event of negative diagnostic imaging and absence of effect of medical treatment.		B
Laparoscopic inspection of suspected endometriosis must be supplemented with biopsy for histological verification of the diagnosis.		B
Anterior compartment: In expert hands, TVUS seems equivalent to MRI for the diagnosis of DIE involving the bladder and ureters. Due to low sensitivity, one may consider supplementing TVUS with MRI if DIE is suspected.		B
Posterior compartment: In expert hands, TVUS and MRI appear to be equivalent for diagnosing DIE involving the rectovaginal septum, sacrouterine ligaments, and vagina. Both TVUS and MRI show limited sensitivity for DIE in the posterior compartment. Provided the scan is performed at an expert level, TVUS and MRI can be used to diagnose DIE in the rectosigmoid.		B
The use of IDEA or the #Enzian-score during TVUS will reduce the heterogeneity of reporting and may improve the diagnostic performance due to a more structured approach.		D
If an ultrasound examination shows: Negative "sliding sign", "kissing ovaries" or bilateral endometriomas, the patient should be referred to a tertiary center if it is not possible to treat the symptoms medically or if there is a fertility desire.		D
Preoperatively, both TVUS and MRI can be performed in patients with DIE to improve surgical preparation.		D
It is important that the MRI scan is performed according to an endometriosis protocol to obtain the best possible images for analysis.		D
Endometriotic nodules in the colon is mainly localized to the rectum or the rectosigmoid segment, and can therefore be diagnosed with TVUS with great certainty.		C
The majority of patients with DIE oral to the rectosigmoid also have nodules in the rectum or		D

rectosigmoid segment.		
It is validated to measure the distance from the anocutaneous transition to the lower edge of endometriosis in the rectum/rectosigmoid with TVUS.		A
The primary investigation of subcutaneous endometriosis consists of obtaining medical history and objective examination supplemented with 2D ultrasound.		C
In the case of inconclusive findings and lesions in the subcutis > 3 cm, MRI is recommended as a preoperative assessment of the extent of endometriosis in relation to fascia and muscle tissue, in order to optimally plan the surgical treatment.		C
CT can be used in cases where MRI is not available at the facility.		D
Thoracic endometriosis syndrome should be suspected in women with endometriosis with recurrent/cyclical pneumo- or hydrothorax.		C
Unlike CT, MRI can distinguish endometriosis in the thorax from other pathology. However, a negative result cannot exclude superficial endometriosis in women with relevant symptoms.		C
As endometriosis in the lumbosacral nerves is rare, in case of relevant symptoms, a neurological examination as well as ultrasound and MRI should be performed to exclude differential diagnosis.		B
MRI should be performed if endometriosis involving the lumbosacral nerves is suspected regardless of the time in the menstrual cycle.		B
The EFI score is a valid estimate of the chance of achieving a spontaneous pregnancy within 36 months after a surgical intervention for endometriosis.		A
ENZIAN and #Enzian scores are valid tools for describing DIE.		A
#Enzian is a valid tool for describing disease dissemination.		A
The ENZIAN score is correlated to pain and operation time as well as risk of complications after surgery and time of hospital stay.		A
The AAGL score is valuable when assessing the surgical difficulty.		B
The AFS/rASRM score has an acceptable reproducibility.		B

The AFS/rASRM score is not consistently associated with symptoms.		B
The UBESS score is externally validated but not usable in its current form.		A
CA-125 should not be used for diagnosing endometriosis		B
Competence in diagnosing endometriosis in the posterior compartment using TVUS can be achieved after 50-60 scans, provided there is a coherent training program at a tertiary centre.		C
A possible training program could consist of familiarization with the consensus put forward by IDEA, theoretical teaching, video demonstration, patient demonstration, and supervision of ultrasound examination on selected patients.		B

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Link to accepted and published guideline https://www.dsog.dk/s/Endometriose-diagnostik-og-udredning.pdf

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