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Diagnostic Challenges and Innovations in Thoracic Endometriosis (TE): Exploring the Role of Imaging and Biomarkers. A narrative review

Julia Bałoniak[1]*, Zofia Szymańska[2], Agnieszka Leszyńska[1], Zuzanna Bałoniak[3], Aleksandra Jonkisz[1], Gabriela Skurzyńska[4], Aleksandra Stremel[5], Michalina Doligalska[6]

Authors' affiliation:

1. University Hospital in Poznań, Przybyszewskiego 49, 60-355 Poznań, Poland
2. Poznan University of Medical Sciences, Collegium Maius, Fredry 10, 61-701 Poznań, Poland
3. Warsaw Southern Hospital, Rotmistrza Witolda Pileckiego 99, 02-781 Warszawa, Poland
4. District Health Center in Otwock, Batorego 44, 05-400 Otwock, Poland
5. Centre of Postgraduate Medical Education, Orłowski Hospital, Czerniakowska 231, 00- 416, Warsaw, Poland
6. Medical Hospital in Garwolin, Lubelska 50, 08-400 Garwolin, Poland

*corresponding author

Julia Bałoniak
University Hospital in Poznań, Przybyszewskiego 49, 60-355 Poznań, Poland
jj.baloniak@gmail.com
ORCID: https://orcid.org/0009-0002-8843-2117
* Author to whom correspondence should be addressed

Zofia Szymańska
Poznan University of Medical Sciences, Collegium Maius, Fredry 10, 61-701 Poznań, Poland
zofia.szymanska2000@gmail.com
ORCID: https://orcid.org/0009-0004-5046-7618

Agnieszka Leszyńska
University Hospital in Poznań, Przybyszewskiego 49, 60-355 Poznań, Poland
agaleszyn@gmail.com
ORCID: https://orcid.org/0009-0005-9568-5659

Zuzanna Bałoniak
Warsaw Southern Hospital, Rotmistrza Witolda Pileckiego 99, 02-781 Warszawa, Poland
zbaloniak@interia.pl
ORCID: https://orcid.org/0009-0006-6968-8781

Aleksandra Jonkisz
University Hospital in Poznań, Przybyszewskiego 49, 60-355 Poznań, Poland
olajonkisz@gmail.com
ORCID: https://orcid.org/0009-0000-7263-9741

Gabriela Skurzyńska
District Health Centre in Otwock, Batorego 44, 05-400 Otwock, Poland
gskurzynska@gmail.com
ORCID: https://orcid.org/0009-0004-5830-7328

Aleksandra Stremel
Centre of Postgraduate Medical Education, Orłowski Hospital, Czerniakowska 231, 00-416, Warsaw, Poland
ola.stremel@gmail.com
ORCID: https://orcid.org/0009-0005-1055-3818

Michalina Doligalska
Medical Hospital in Garwolin, Lubelska 50, 08-400 Garwolin, Poland
michalina.doligalska1@gmail.com
ORCID: https://orcid.org/0009-0002-1480-0677

ABSTRACT
Endometriosis is a condition characterized by endometrial tissue in ectopic locations outside the gynecological organs. Thoracic endometriosis (TE) is a rare condition, manifesting as cyclical respiratory symptoms. Diagnosis of TE is often delayed because of its non - specific symptoms. Improvements in imaging techniques and biomarker research offer hope for improving the diagnosis of TE. High - resolution imaging modalities, such as high - resolution computed tomography (HRCT) and magnetic resonance imaging (MRI), provide detailed visualization of pleural and pulmonary lesions and leverage hormonal responsiveness for dynamic imaging during the menstrual cycle. Using new biomarkers, like cystatin C, CA-125 and microRNA (miRNA), can increase the use of non - invasive diagnostic methods to define the severity of a patient's disease and invent treatment plans. Early diagnosis and treatment of TE are vital to prevent severe complications. It can also help to reduce the burden of chronic pain and improve patient's quality of life, leading to more effective management of this under-diagnosed condition. The aim of this paper is to explore current and upcoming diagnostic possibilities for TE, mainly through the lens of advanced diagnostic innovations, and assess their potential to improve outcomes for patients with this complex condition.

Keywords: Thoracic endometriosis, endometriosis, diagnosing, imaging, biomarkers

Introduction

Endometriosis is a condition in which endometrial-like glands and stroma occur ectopically, outside the gynecological organs [1,2]. It is estimated that 1 to 5% of women in reproductive age suffer from endometriosis [3]. While describing endometriosis, an uncommon but important type of it should be mentioned, namely the extra - pelvic endometriosis (EPE). The EPE is fairly a rare condition, thus its precise prevalence is still unknown, but estimated to range between 1 to 12% of patients diagnosed with pelvic endometriosis. [4] Although EPE has a broad range of clinical presentations, in this article, a focus will be placed on its major type, that is thoracic endometriosis (TE).

TE is a rare condition in which endometrial tissue is present in the thoracic cavity, leading to a wide range of symptoms and manifestations. The Fprevalence range of this condition is reported to be around 1% of the patients with endometriosis, however the exact frequency is yet to be determined due to the fact that it is still often mis or underdiagnosed [1]. Even though the percentage of patients with endometriosis who develop TE is low, it is still the most common location of extrapelvic endometriosis. [1,2,5] The clinical presentation of TE consists of a whole variety of symptoms, which are usually related to the anatomic location of the ectopic endometrial lesions. However the most common manifestations are catamenial pneumothorax, catamenial hemothorax, catamenial hemoptysis and pulmonary nodules, which altogether are described as thoracic endometriosis syndrome (TES). It is important to highlight the significance of the temporal relationship of the symptoms with menses, as the early clinical presentations can be nonspecific, therefore a different, more common diagnosis might be made[1]. Apart from the time range in which the symptoms occur, also such features as young age, coexistence of another recurrent disease, domination of right-sided manifestations and a history of infertility can indicate a higher probability of the TE diagnosis [2].

Even with the recent advances in the diagnostic field, detecting TE itself still remains a challenge and it is often delayed until the symptoms' temporal relationship with menses is recognized. In addition, an important factor making EPE diagnosis extremely difficult is the occurrence of endometriotic lesions distantly from gynecological organs, which further complicates the diagnostic process. As a result, delays in arriving at the correct diagnosis and implementing an appropriate treatment are often observed, which highlights the need for an multidisciplinary approach. Therefore the diagnostic methods of TE will be evaluated in this article [1]. Each of those has its advantages and disadvantages which will be evaluated in this article along with the current and innovative diagnostic methods.

Overview of thoracic endometriosis

TE is an uncommon condition defined by the presence of endometrial tissue in the pleura, lung parenchyma, and respiratory tract. TE accounts for only 1% of all endometriosis cases, although the respiratory system is the most common location of extrapelvic endometriosis. [6] There is not enough data to determine the exact frequency of pulmonary endometriosis, although it is assumed that there is a large underdiagnosis of this disease. The pathogenesis of TE is not fully clear, but there are few theories that try to explain the appearance of thoracic endometriosis. First theory is called coelomic metaplasia. It was proposed by Ivanoff and assumes that cells located in the respiratory organs, under the influence of some physiological factors, such as estrogen, could undergo metaplasia into endometrium - like cells [7,8] The most prominent theory is retrograde menstruation theory, presented by Sampson [9]. It assumes that endometrial cells travel in a retrograde movement through the fallopian tubes. Peritoneal fluid carrying these cells flows toward the diaphragm, where the cells either implant on the diaphragmatic surface or migrate through holes in the diaphragm into the pleural cavity. This migration may occur through congenital or acquired fenestrations in the diaphragm [5, 10]. Third, prostaglandin theory proposes that high level of prostaglandin F2α during menstruation can lead to constriction of blood vessels, accompanied by necrosis of lung tissue and spasms in the bronchial airways. This may cause the rupture of alveoli in pre-existing subpleural blebs and bullae, leading to the characteristic presentation of catamenial pneumothorax [7,11,12]. Last is lymphatic and hematogenous dissemination theory which suggest that ectopic endometrial benign metastasis arise from the spread of endometrial cells through the lymphatic or hematogenous pathways. That could explain endometrial lesions in the bronchopulmonary region [13]. There are various clinical presentations of TE. The term *Thoracic Endometriosis Syndrome (TES)* refers to the clinical manifestations resulting from TE. The most common symptoms in TES are chest pain and dyspnea [14]. Pneumothorax is the most prevalent clinical complication associated with TES. When it occurs in relation to menstruation, it is diagnosed as catamenial pneumothorax [15]. Other conditions characteristic of TES include hemothorax and hemoptysis. Recognizing the association between the patient's symptoms and their menstrual cycle is crucial for an accurate diagnosis [16].

Diagnostic Challenges

Among the main clinical presentations of TE, the most common is catamenial pneumothorax (CP), which is developed by over 70% of patients. To state a CP it is required for a pneumothorax to be recurrent, and happen within 72 hours from the onset of menstruation. Over 90% of CP are known to be located on the right side, and account for over 20% of spontaneous pneumothorax among reproductive-aged women. The manifestations of pleural CP commonly consist of cough, dyspnoea, chest pain, and shortness of breath, which also frequently occur in many other disease entities, such as lung cancer or pleurisy which need to be taken under account in a differential diagnosis [2]. It is also important to mention hemoptysis, a less common but equally important symptom as the previously mentioned ones, while being aware of its other possible causes, such as tuberculosis, chronic bronchitis, pulmonary infarction, bronchial carcinoid, arteriovenous malformation and abnormal blood vessels, with which TE should always be differentiated [17]. Concerning diaphragmatic TE, the main complaint commonly presented by the patients is shoulder pain, which is characteristically located on the patient's right side. Apart from the respiratory tract symptoms, TE patients may also present typical gynecological manifestations of endometriosis such as dyspareunia, chronic pelvic pain, dysmenorrhea and ovarian endometriomas. Moreover, although it is not frequent, patients with severe endometriosis may also develop hemorrhagic ascites, which followed by pleural effusions and elevated levels of marker CA125 may easily lead to a better known diagnosis, that is Meigs syndrome or ovarian cancer [18,19]. The importance of including TE in the differential diagnosis also pertains to fertility. While treatment for ovarian cancer often leads to infertility, TE can be successfully treated, preserving the patient’s potential to have a child [18]. Referring to the challenges in diagnosing TE it is important to highlight the fact that many patients with this condition may be asymptomatic, which can further delay the diagnosis. Moreover, the lack of awareness of existing such disease entity as TE is an important factor due to which many patients with TE are misdiagnosed or remain without any diagnosis at all.

Advances in Imaging Techniques

Progress in imaging techniques has played a massive role in improving the diagnosis and management of TE. These advancements span both current practices and emerging innovations, with varying strengths and limitations in terms of sensitivity, specificity, and accessibility. Currently, mostly used imaging techniques in TE diagnosis include Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and video - assisted thoracoscopic surgery (VATS). CT imaging is widely used in diagnosing thoracic conditions and is often the first-line imaging method for TE - related complications such as pneumothorax, hemothorax, or pleural effusions [20]. CT images in TE may include opacities, nodular abnormalities, thin-walled cavities, and bullous structures [21]. Diaphragmatic implants present as hypo-attenuating areas. However, CT has low specificity for endometrial lesions and cannot reliably differentiate TE from other thoracic conditions [22]. MRI offers superior soft tissue contrast compared to CT and can help identify endometrial implants in the pleura or diaphragm. T1 - weighted imaging is particularly effective for detecting small pleural endometriomas, as it highlights cystic hyperintense lesions on the visceral or parietal pleura [23].

Chest MRI can be a valuable diagnostic tool, especially for individuals experiencing isolated catamenial chest pain who are being evaluated for video-assisted thoracoscopic surgery (VATS) [23]. Despite its advantages, MRI is less readily available in emergency settings and is typically used as a supplementary diagnostic tool. The method of choice for a definitive diagnosis of TE is VATS [24]. In the review of 195 patients with catamenial pneumothorax done by Korom et al., based on VATS results, 52.1% were diagnosed with TE [11]. The literature describes a variety of findings observed during VATS, such as diaphragmatic defects, diaphragmatic implants, implants on the visceral and parietal pleura, parenchymal implants, blebs, and bullae [15]. VATS function as both a diagnostic and therapeutic procedure. The lack of findings on imaging tests does not eliminate the necessity of examining the upper abdomen, particularly the diaphragm, during a minimally invasive surgical procedure [20].

Using high-resolution imaging techniques, such as high-resolution computed tomography (HRCT), has increased the ability to detect subtle abnormalities associated with TE, particularly in the lungs. HRCT provides a more precise depiction of the fine morphological details of lung disease and allows for detailed visualization of pleural, diaphragmatic, and parenchymal lesions, offering critical information for preoperative planning and patient counseling. Often, when chest X-ray, bronchoscopy, and angiography fail to reveal signs of the disease, CT proves more helpful in establishing the diagnosis. However, HRCT is superior to standard CT due to its improved spatial resolution [25,26,27].

An exciting development in the field is the use of dynamic imaging studies conducted at different phases of the menstrual cycle. This approach leverages the hormonal responsiveness of endometriotic tissue to detect cyclical changes in the thoracic cavity [28]. Such temporal imaging enhances diagnostic accuracy and offers a non-invasive method to corroborate clinical suspicion of TE. However, more research is needed in this area. Botterill et al. conducted a study to determine whether the menstrual cycle affects MR imaging in endometriosis. The results showed no significant differences in image quality, disease extent, or disease severity between MR imaging performed during menstruation and outside of it [29]. On the other hand, studies conducted specifically on TE often highlight the importance of performing examinations during menstruation, as this is when lesions are more likely to become visible [1]. For instance, a study by Rousset et al., which evaluated MRI for diaphragmatic endometriosis diagnosis, showed differences in results that could likely be attributed to the timing of the menstrual cycle [30]. This highlights the need for further research in this field.

Role of Biomarkers

The process of diagnosing TE presents numerous challenges. Biomarkers, particularly CA-125 (Cancer Antigen 125) and various inflammatory markers, have become valuable tools for diagnosing and monitoring TE. CA - 125, a well-known biomarker primarily used in the diagnosis and management of ovarian cancer, has also been linked to endometriosis, including the thoracic form of the disease [31]. Women with TE typically exhibit significantly elevated levels of CA-125 compared to those without the condition.

Although not specific to TE, elevated CA - 125 can serve as a helpful indicator, especially when its levels are monitored over time or used alongside other diagnostic methods, such as imaging and clinical evaluations.

For instance, elevated CA - 125 levels in a woman presenting with spontaneous pneumothorax may raise suspicion of TE in the appropriate clinical context [23, 32]. However, one of the limitations of using CA - 125 for diagnosing TE is its lack of sensitivity and specificity, as elevated levels can also occur in other conditions.

Endometriosis is inherently an inflammatory condition, prompting research into the role of inflammatory markers in its diagnosis. When endometrial-like tissue implants in the thoracic cavity, it triggers a local immune response, releasing pro-inflammatory cytokines and other mediators. Measuring inflammatory markers in the blood can help detect this underlying process, offering a non-invasive adjunct to other diagnostic methods.

C-Reactive Protein (CRP), a general marker of inflammation, is often elevated in conditions involving an inflammatory response.

The diagnostic significance of hs - CRP in endometriosis was assessed by Thubert et al., who concluded that hs - CRP levels are not useful for diagnosing or staging endometriosis [33]. Therefore, assumption can be made, that CRP levels would likely be non - diagnostic in TE as well.

Cystatin C is another valuable biomarker primarily used to assess kidney function, with potential applications in identifying cardiovascular and systemic diseases. Its role as a marker in endometriosis has also been explored. A study published in 2023 reported that increased cystatin C levels could be used as a diagnostic guide for patients with advanced endometriosis [34]. This finding suggests a potential role for cystatin C in diagnosing TE, although further research is needed to confirm that assumption.

The connection between microRNA (miRNA) levels and endometriosis has gained significant attention recently. MicroRNAs are small, non - coding RNAs that regulate gene expression post - transcriptionally. Dysregulated miRNA expression has been linked to endometriosis, with specific miRNAs associated with the development and progression of the disease [35]. Circulating miRNAs found in serum, plasma, or pleural fluid are emerging as promising non-invasive biomarkers for TE. For instance, miRNAs involved in inflammation, angiogenesis, and tissue remodeling could indicate the presence of ectopic endometrial tissue in the thoracic cavity. However, a significant limitation in studying miRNA as biomarkers is the small patient group and insufficient representation of all endometriosis stages [36]. It is essential to continue the study to explore the potential of using biomarkers to diagnose and treat TE.

Discussion and conclusion

Endometriosis is a complex disease that significantly impacts women's health. Despite its prevalence, it remained under - recognized for many years. Fortunately, awareness has been increasing in recent years. However, extra - pelvic endometriosis, such as TE, continues to receive limited research attention and remains a diagnostic challenge due to its non-specific symptoms. As highlighted in this research, recent advancements in diagnostics - particularly in imaging techniques and biomarker studies - have the potential to transform how TE is identified and managed.

High - resolution imaging modalities, such as HRCT and MR, have greatly improved the ability to detect TE. HRCT provides detailed visualization of pleural and parenchymal lesions.

The role of MR in diagnosing endometriosis, particularly its application during different phases of the menstrual cycle, remains under-researched. Dynamic imaging during different phases could reveal cyclical changes in the thoracic cavity. This promising field warrants further investigation to determine its full potential. Biomarkers, such as CA - 125 and emerging molecular indicators like microRNAs (miRNAs), offer promising non - invasive diagnostic tools. Elevated levels of CA - 125 have been observed in patients with TE, although its lack of specificity remains a limitation. On the other hand, circulating miRNAs in serum, plasma, or pleural fluid could provide a more precise and less invasive diagnostic alternative. The role of cystatin C in TE also needs more research. All of these diagnostic advancements could facilitate earlier and more accurate diagnoses, reducing the need for invasive procedures like VATS.

Implementing new imaging techniques and biomarkers can not only improve the identification of affected patients but also significantly influence treatment strategies. For instance, biomarkers could be used to monitor disease progression or evaluate responses to therapy, paving the way for personalized treatment plans. Meanwhile, new imaging techniques could guide minimally invasive procedures and assess the efficacy of hormonal or surgical interventions. Early and accurate diagnosis enabled by these innovations would also help reduce complications, such as recurrent pneumothorax or pleural adhesions, ultimately improving patient outcomes.

Barriers to implementing new methods of diagnosis include accessibility. For instance, a greater number of hospitals are equipped to perform chest X - rays for detecting catamenial pneumothorax compared to HRCT. Another limitation is cost, which tends to be higher for advanced diagnostic methods as well as for less commonly used, specific biomarkers like cystatin C. Clinician training also poses a potential challenge. Clinicians require training to understand the optimal timing and methods for examining patients with TE to achieve accurate diagnoses.

Considering endometriosis as a condition that affects the whole organism, not only the gynecological organs, is a crucial element of raising the awareness of EPE and its potential manifestations beyond the pelvis. Furthermore, patients should also be informed that due to endometriosis, specifically its extra - pelvic presentation, manifestations from the respiratory tract may also occur. This information could help them recognize the connection between the symptoms and their menstrual cycle much earlier. Also, among patients diagnosed with pelvic endometriosis and treated by video laparoscopy, it is highly recommended to carefully examine the diaphragm in order to identify any potential endometrial lesions. In order to diagnose TE earlier, clinicians should maintain a high level of suspicion while diagnosing women of reproductive age or those undergoing hormone replacement therapy who present with such symptoms as cyclical chest pain, shortness of breath and/ or hemoptysis. All these measures can significantly improve not only the diagnostic process but also the quality of life for patients affected by the disease.

Disclosure

Author' s contribution:

Conceptualization: JB;
Methodology: GS, AJ;
Software: MD, AJ, AS;
Check: JB;
Formal analysis: ZS, ZB;
Investigation: ZS, AJ;
Resources: MD, AS, GS;
Data curation: AS, MD, ZB;
Writing - rough preparation: JB, ZB;
Writing - review and editing: JB, ZS;
Visualization: JB;
Supervision: JB, ZS;
Project administration: JB;

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