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Thoracic endometriosis – multidisciplinary approach to diagnosis and treatment (Literature review)

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Worldwide, the prevalence of endometriosis among women of reproductive age is approximately 10%. This pathology is often accompanied by damage to the pelvic organs, primarily the reproductive system, and is manifested by pain syndrome (dysmenorrhea, dyschezia, chronic pelvic pain, dyspareunia, dysuria), abnormal uterine bleeding, infertility. However, the spread of endometriosis lesions also occurs outside the pelvic cavity and abdominal cavity (lesions in the intestines, peritoneum, bladder, ureters). Extragenital foci can be found in the tissue of the diaphragm, lungs, pleura, skin. Thoracic endometriosis is manifested by damage to the pleura and lungs. Given that thoracic endometriosis is a pathology that is not common, there is not a sufficient number of publications in the scientific literature that would cover the data of hundreds of patients with thoracic endometriosis. The vast majority of reports are the descriptions of clinical cases. This article presents clinical cases of various forms of thoracic endometriosis in patients of different ages. Often this disease is accompanied by such clinical symptoms as cough, hemoptysis, shortness of breath, chest pain. Such manifestations can last for several months and often coincide with the onset of menstruation. Patients are primarily diagnosed with pneumothorax, hemothorax. Often the diagnosis of thoracic endometriosis is not fast and takes a period from several days to months. Visual diagnostic methods – chest radiography, computed tomography, magnetic resonance imaging, bronchoscopy, video-assisted thoracoscopy – are among the main diagnostic methods. Taking a tissue biopsy with a histological conclusion is crucial for confirming the diagnosis of thoracic endometriosis. Often this extragenital form of endometriosis is combined with endometriosis of the uterus, ovaries, fallopian tubes and peritoneum.
Treatment of endometriosis includes surgical intervention with appropriate surgical correction and removal of endometrial foci. To prevent recurrence of pathology, patients often receive a consultation of gynecologist with recommendations to use hormonal therapy – combined oral contraceptives, gonadotropin-releasing hormone agonists, progestogens.
Only a multidisciplinary approach involving doctors from different specialties (family doctor, surgeon, radiologist, gynecologist) is the most effective for the diagnosis and treatment of thoracic endometriosis with the lowest frequency of recurrences in the future.
Keywords: *endometriosis, thoracic endometriosis, clinic, pathogenesis, diagnostics, treatment.*

Торакальний ендометріоз – мультидисциплінарний підхід до діагностики та лікування (Огляд літератури)

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У всьому світі поширення ендометріозу серед жінок репродуктивного віку перебуває на рівні близько 10%. Ця патологія часто супроводжується ураженням органів малого таза, передусім репродуктивної системи, і проявляється больовим синдромом (дисменорея, дисхезія, хронічний тазовий біль, диспауренія, дизурія), аномальними матковими кровотечами, безпліддям. Проте поширення ендометріоїдних вогнищ спостерігається і поза порожниною малого таза та черевною порожниною (ураження кишечника, очеревини, сечового міхура, сечоводів). Екстрагенітальні вогнища можуть виявлятись у тканині діафрагми, легень, плеври, шкіри.
Торакальний ендометріоз проявляється ураженням плеври та легень. З огляду на те що торакальний ендометріоз є патологією, яка трапляється не часто, то в науковій літературі немає достатньої кількості публікацій, які б охоплювали дані сотень пацієнтів із торакальним ендометріозом. Переважна більшість повідомлень становить опис клінічних випадків. У цій статті наведені клінічні випадки різних форм торакального ендометріозу в пацієнтів різного віку. Часто захворювання супроводжується такими клінічними симптомами, як кашель, кровохаркання, утруднення дихання, біль у грудній клітці. Такі прояви можуть тривати кілька місяців і часто збігаються з появою менструацій. Першочергово в пацієнтів діагностують пневмоторакс, гемоторакс. Часто діагностика торакального ендометріозу не є швидкою і займає період від кількох днів до місяців. Методи візуальної діагностики – рентгенографія органів грудної клітки, комп'ютерна томографія, магнітно-резонансна томографія, бронхоскопія, відеоасистована торакоскопія – належать до основних діагностичних методик. Взяття біопсії тканин із гістологічним висновком є вирішальним для підтвердження діагнозу торакального ендометріозу. Нерідко ця екстрагенітальна форма ендометріозу поєднується з ендометріозом матки, яєчників, маткових труб та очеревини.
Лікування ендометріозу включає хірургічне втручання з відповідною оперативною корекцією та видалення ендометріальних вогнищ. Для запобігання рецидиву патології пацієнти часто отримують консультацію гінеколога з подальшим призначенням гормональної терапії – комбінованих оральних контрацептивів, агоністів гонадотропін-рилізинг-гормонів, прогестагенів.
Тільки мультидисциплінарний підхід із залученням фахівців різних спеціальностей (сімейний лікар, хірург, радіолог, гінеколог) є найефективнішим для діагностики та лікування торакального ендометріозу з найменшою частотою випадків рецидивів у майбутньому.
Ключові слова: *ендометріоз, торакальний ендометріоз, клінічна картина, патогенез, діагностика, лікування.*

Endometriosis is a chronic disease with inflammatory component and the existence of endometrium tissue outside of uterus [1]. Till 10% of women in reproductive age suffer from endometriosis [1, 2]. Nowadays, there is no doubt about the impact of endometriosis on numerous woman's activities – daily functioning, health, psychological well-being, etc.

Many theories explain the development of endometriosis. The theory of retrograde menstruation blood through the fallopian tubes describes the dislocation of endometrium tissue outside the uterus in other organs [3–5]. This theory explains the presence of endometrium lesions in diaphragm, chest, pleura, other extragenital organs. The endometrium tissue can pass through lymphogenic and hematogenic ways to the thorax cavity (metastatic theory). The coelomic metaplasia theory presents the position that there is a metaplasia of mesothelial cells in pleura, peritoneal surfaces into endometrial tissue, stroma, gland [3–5]. Immune disbalance can impact on the endometriosis development. This theory is supported by the elevated secretion of cytokines, prostaglandins, induced by the inflammatory response, which led to the changes in different tissues.

Also, there is an association of endometriosis development with genetic predisposition [6, 7], hormonal disorders [8], gut and vaginal microbiota changes [9–11]. Many gynecological diseases such as polycystic ovary syndrome [12], infertility [13], premenstrual syndrome [14–19], uterine fibroid [20, 21] have common hormonal changes typical for endometriosis diseases and related to estrogen-progesterone imbalance [8]. Also, there is an association between metabolic syndrome and some gynecological pathologies, including endometriosis, polycystic ovary syndrome, uterine leiomyoma, infertility [22–28], which can be explained by specific plasma metabolites action such as triglycerides, high and very low-density lipoprotein metabolites, acetone, 3-hydroxybutyrate, cholesterol, etc. [22]. Commonly, endometriosis is considered the disease of women of reproductive age. But it impacts on different periods of female life – adolescence, pregnancy course and outcomes, menopause [1, 29–31]. The common symptoms of endometriosis are associated with dysmenorrhea, infertility, chronic pelvic pain, abnormal uterine bleeding, etc. [1].

In 1979 the American Society for Reproductive Medicine (ASRM, then known as the American Fertility Society) has proposed the classification of the abdominal endometriosis [32]. This classification was revised several times and describes the damage to peritoneum, ovaries and tubes. According to it there are deep and superficial forms of endometriosis and 4 stages of endometriosis – minimal (I stage), mild (II stage), moderate (III stage) and severe (IV stage). ENZIAN classification of deep endometriosis helps to recognize the distribution and deep of endometriosis lesions in pelvic cavity and outside, it describes the presence of endometriosis lesions in bladder, rectum, ureter, diaphragm, lungs, nerves [33]. It helps a lot for doctors gynecologists and other physicians both for correct diagnosis and treatment [34].

As to the extragenital forms of endometriosis, the review of literature demonstrated that the most spread extragenital form of endometriosis is the gastrointestinal one [35]. Its rate is 23% among patients with deep infiltrative endometriosis. The most often damage locations are rectosigmoid colon, appendix, small intestine. Endometriosis of urogenital tract is on the second position of endometriosis spread, in which 85% of all lesions are located in the bladder [35]. Also, the endometriosis of nerves and skin can be occurred.

As to the thoracic endometriosis syndrome (TES), it is considered to be a rare situation. According to the results of the review, the most localization of endometriosis cells and damage to diaphragm (44.5%), pleura (12.7%) and the lungs (4.5%) [35]. Despite that extragenital endometriosis is a common disease in clinical practice, very often there is a delay in correct diagnosis of it. A. Wetzel et al. inform that in 50 patients with thoracic and diaphragmatic endometriosis, the average period from manifestations onset to diagnosis was 47 months (0–212) [36].

According to the results M. Agossou et al. the rate of annual cases of TES is 1.1 incident / 100,000 persons [37]. At the same time the frequency of annual cases of TES in reproductive age women (15–45 years) was higher – 6.9/100,000 and prevalence – 1.2/1,000 [37]. There are no opened multicentral clinical studies about TES. Mostly the scientific publications present the clinical cases of the patient with this pathology [38–41].

There are 2 forms of TES, such as pleural and pulmonary [1]. Pleural form can be manifested as catamenial pneumothorax, catamenial hemothorax, and non-catamenial endometriosis-related pneumothorax. Pulmonary form included catamenial hemoptysis and lung nodules [1]. J. H. Lee et al. inform about two types of thoracic endometriosis: pneumothorax or hemothorax with damages of pleura and pneumothorax or hemothorax with damages of lung parenchyma [42]. According to S. Fukuda et al., TES includes catamenial pneumothorax, endometriosis-related pneumothorax, and catamenial hemoptysis [43]. Most of the cases (94.4%) of TES were connected with damage to right side [43]. M. P. Andres et al. have performed a multicentral descriptive research which included 5,465 articles and 179 articles, mostly case reports about extrapelvic deep endometriosis [44]. Among them, 628 articles were devoted to TES. The scientists inform that 80% of all cases are occurs on the right side of diaphragm, pleura and lungs.

As to the reproductive disorders in women with thoracic endometriosis, a strong association was found between high frequency of infertility, severe pelvic endometriosis and thoracic endometriosis [45].

The thoracic endometriosis can be manifested by different symptoms – pain, menstrual cycle-related (catamenial) pneumothorax, hemothorax, hemoptysis [46]. M. Agossou et al. studied the clinical manifestations of patients with TES [37]. Among 479 cases of pneumothorax for the period 1 January 2004 and 31 December 2020 there were 222 (44%) female patients; 63 (30%) of those women were diagnosed catamenial pneumothorax (pneumothorax and hemopneumothorax); 71 women were diagnosed TES (49 cases of pneumothorax, 14 – hemopneumothorax and 8 – hemothorax).

According to the results of T. Marjanski et al. mostly, the patients with endometriosis can have chest pain (96%), cough (52%), hemoptysis, dyspnea (67%) [47]. Symptoms are usually related to the menstruation days. A review of scientific publications, K. Nikolettos et al. have analyzed

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202 researches that involved 592 patients with thoracic endometriosis [48]. The patients were in active reproductive age (33.8 years old – median age), only 2 women were much older – 51 and 74 years old, respectively. The most typical symptoms were pneumothorax (68.4%), chest pain (22.0%), dyspnea (20.9%), hemoptysis (14.2%). 53.5% of patients had gynecological operations and 8.5% – cesarean section.

The duration of chest pain can vary for different periods. In a clinical case, presented by J. O. Ogunkoya et al., a patient with a 22-year history of chest pain duration and a 20-year history of cough which appeared periodically related to menstruations [49]. The patients visited different clinical for many years to relief her symptoms.

In a systematic review, 142 articles about pleural effusion which was associated with endometriosis were analyzed [50]. These articles included information about 176 patients of reproductive age. The women complained of dyspnea (67%), chest pain (55%), abdominal pain (40%). In most of the cases, there was a unilateral pathology. In 74% the results of histology of pleura tissue confirmed endometriosis.

The age of 60 patients with thoracic endometriosis who admitted in Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico (Milan, Italy), was more – 41.4 ± 7.1 years [51], but the age of the diagnosis was 34.5 ± 7.3 years. Most of the patients never smoked (67.3%). 83.3% of them had endometriosis of other organs and systems. Only 75% of patients manifested with catamenial symptoms like pneumothorax (41.6%), shoulder pain (38.3%), pleuritic pain (28.3%), etc.

A clinical case was described by K. E. Udoh et al., in which the authors present a situation of a woman who had a primary suspicion for Meig's syndrome and cancer of ovary [39]. After laboratory test, hematological data, ultrasound examination, computer tomography (CT) of chest, pelvis, abdominal cavity, levels of oncoproteins, several thoracenteses, examination of pleural fluid, video-assisted thoracoscopy with right robotic-assisted pleurectomy, pleura biopsy with histological study, the patient was diagnosed thoracic endometriosis. The duration of all examinations lasts for 2 weeks.

Another clinical case is presented by V. Mhezi et al. [40]. The authors describe a case of a 34-year-old woman, who have suffered from pelvic pain and heavy menstrual bleeding for 6 years, chest pain related to menstruation for 5 years, very often she had pneumonia. The patient was suspected for pulmonary tuberculosis. And the last period she manifested with blood cough. After an analysis of pleura fluid, Gene Xpert for MTB (*Mycobacterium tuberculosis*), detection of cancer antigen-125 (CA-125), X-ray and CT of chest, abdominal laparotomy in which endometrial cysts and salpingitis were diagnosed. The woman received hormonal therapy and progress of recovery.

But also, there are cases of rapid diagnosis of TES [41]. A woman of 33 years old admitted to the clinic with symptoms of cough and shortness of breath which appeared only 2 days before. No complaints of pelvic endometriosis symptoms. She had a positive family history of endometriosis. After CT and X-ray examination of chest, study of pleural effusion, CA-125, the patient was diagnosed thoracic endometriosis. A surgical treatment (incision of endometriosis lesions from diaphragm) and hormonal treatment with gonadotropin-releasing hormone for 6 months led to absence of pleural effusion in control chest X-ray examination. The patient was prescribed danazol.

Also, the clinical cases of combination of pelvic and thoracic endometriosis are presented. C. Wong et al. have described a case of the 40-year-old woman who had only dyspnoe by physical overload [52]. Any other respiratory symptoms like pain, menstrual cycle-related (catamenial) pneumothorax, hemothorax, hemoptysis were absent. But the patient suffered from pelvic endometriosis. CT revealed pleural infusion on the right side, the woman was performed thoracoscopy and biopsy of pleura and histological result confirmed endometriosis and TES. Similarly, a clinical case of another combination – endometriosis of abdominal wall and thoracic endometriosis is presented by B. Gao et al. in a woman who had 2 cesarean sections but no any form of pelvic endometriosis [53].

Several benign gynecological diseases can be related to the pleural effusion. Among them there are endometriosis, ovarian hyperstimulation syndrome, Meig's syndrome [54, 55]. The pleural effusion can be explained by various theories of endometriosis development – retrograde menstruation blood, metastatic theory, coelomic metaplasia theory. The damage to pleura, lung parenchyma, diaphragm by endometrium cells can occur in women of reproductive age. The relation of endocrine system and lung pathology is also a relevant issue today. Pleura damage can be related to hypothyroidism, breast cancer, thyroid cancer and lymphangioleiomyomatosis [56].

A case of the 43-year-old woman with only 1 complaint of chest pain and tightness, breathlessness and no signs of cough and hemoptysis [57]. The woman had these complaints for a period of 3 years. Also, she complained of severe menstruations that led to anemia. She underwent chest X-ray, thoracentesis, general blood analysis, CT of thorax and abdominal cavity, thoracic pleural biopsy and histological study of pleura; tissue, carcinoembryonic antigen and CA-125 in blood serum. A large ovarian cyst was diagnosed, pleural endometriosis was confirmed. A patient had surgical treatment, total hysterectomy with bilateral salpingo-oophorectomy.

The other case is presented by K. E. Udoh et al. [39]. The woman, 37 years old, was hospitalized with the complaints of shortness of breath. The symptoms lasted for 2 weeks. The elevated CA-125, decreased hemoglobin were found. After determination of right pleural effusion with adjacent atelectasis/consolidation, the patient underwent CT. She was suspected of lung cancer. Ultrasound-guided thoracentesis was performed, and bloody fluid was received. This procedure was done three times in the hospital in a period of approximately 2 weeks. On CT images, masses of the left ovary were diagnosed. Video-assisted thoracoscopy with right robotic-assisted pleurectomy, pleurodesis, lymph node dissection, intercostal nerve blocks, and a pleural biopsy were performed. A final histological study confirmed endometriosis. The patient was consulted by gynecologist and was well even in 6 months after operation.

The research of F. Pagano et al. studied the rate and typical manifestations of patients with diaphragmatic

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endometriosis and the preoperative characteristic of diaphragmatic endometriosis [58]. In 1,372 patients with endometriosis (which was diagnosed by histological research) who had laparoscopy, a complete review of diaphragm was performed. 65 women (4.7%) were confirmed diaphragmatic endometriosis. These patients had more often complains of infertility (49.2% versus 28.7% of women with only abdominal endometriosis, $p < 0.05$), diaphragmatic pain (27.7% versus 1.8%, respectively), III and IV endometriosis stages according to ASRM. While the frequency of such features as dysmenorrhea, dyschezia, dysuria, and/or dyspareunia was the same in both groups.

Another group of scientists A. Naem et al. confirm that the rate of diaphragmatic endometriosis is 1.85% (23 women among 1,237 patients with pelvic endometriosis which was proven by histology (2019–2022 years)) [59]. The patients with diaphragmatic endometriosis had complaints of dysmenorrheal (68.2%), cyclic upper abdominal pain (60.9%), cyclic chest pain (43.5%), cyclic pain in shoulder (34.8%), dyspaurenia (31.8%), dyschezia (27.3%). As to the symptoms of breath – 17.4% of patients had cyclic apnea and cyclic coughing each. No catamenial pneumothorax was found.

There is an insufficient screening for thoracic endometriosis [59]. There can be some reasons for this like not large number of such patients, only 4% of physicians took history for respiratory symptoms, etc. [60]. There are different diagnostic methods for endometriosis revealed [46]. Usually, a multidisciplinary management is the most effective one [46, 53, 61]. The clinical manifestations of thoracic endometriosis are not specific. In most of the cases, the diagnosis is confirmed by histological results. Imaging methods are the most spread and have good accuracy for TES diagnosis.

CT is the method for good visualization of abdominal endometriosis lesions like ovarian endometrioma, lesions of uterus, bowels, bladder [62] and also in thoracic cavity. X-ray, chest CT, chest magnetic resonance imaging (MRI), and bronchoscopy, video-assisted thoracoscopy, robotic-assisted thoracoscopy can be performed [4]. CT is often performed for pelvic and abdominal endometriosis lesions and tumors [62]. The common finding in chest CT are ground-glass opacities, nodules, pneumothorax, cystic lesions, consolidation, pleural effusion; for chest X-ray examination – pneumothorax, nodules, consolidation, pleural effusion [48]. MRI can be used for diagnosis of diaphragmatic endometriosis, its sensitivity is 78–83% [63]. MRI is not so acute for diaphragmatic endometriosis diagnosis as surgery [64]. However, A. Aiob et al. inform about the limited accuracy of MRI for revealed the superficial and parametrial lesions [65]. A video-assisted thoracic surgery and video laparoscopy are used both for the diagnosis and treatment of TES [3, 4].

Hormonal treatment for TES can be used. Oral contraceptive pills, agonists of gonadotropin releasing hormones, gestagens can be rather effective for the recovery. But the delay of diagnosis and the emergency patient's state usually led to the need for operative procedure. Clinical guidelines in Japan for the extragenital endometriosis treatment recommend performing "Surgical treatment for catamenial pneumothorax may be effective depending on the symptoms" (strength of recommendation is strong – 1, strength of supporting evidence is weak – C) [66]. Also, "Catamenial hemoptysis may be ameliorated by conservative treatment without surgery, but surgery is to be considered when symptoms are severe" (strength of recommendation is weak – 2, strength of supporting evidence is very weak – D) [66]. As for thoracic endometriosis, medical therapy, alone or as postoperative adjuvant therapy, may be considered, depending on the case (strength of recommendation is weak – 2, strength of supporting evidence is weak – C).

J. H. Lee et al. inform that even after surgical treatment, there is a high rate of preumothorax recurrence [42]. That is why multidisciplinary approach of team of surgeons and gynecologists is the most effective [1, 4, 5, 67]. M. J. Porcel et al. inform about that 76% of woman with pleural endometriosis had hormonal treatment, 60% underwent surgical operations [50]. According to the results of review of K. Nikotettos et al. 40.1% of patients with TES out of 220 patients had a combination of hormonal and surgical treatment and 26.8% of them had eve one episode of recurrence [48]. The rate of recurrence in the patients who were prescribed only hormonal treatment was 33.3%. The less recurrence was observed in the cases of combinative treatment (hormonal and surgical approach) [43].

Thus, thoracic endometriosis is a pathology of women which is manifested by various clinical respiratory symptoms which mostly related to the menstrual periods. The signs of pelvic endometriosis can be present, but not always. The duration for diagnosis very often lasts some weeks. The most effective is considered to perform a multidisciplinary team for the diagnosis and treatment of thoracic endometriosis.

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