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## Extra-Pelvic Endometriosis: A Systematic Review

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**Abstract**

Objective: To conduct a systematic review of the literature for patients with extra-pelvic deep endometriosis.

Data source: A thorough search was performed through PubMed/MEDLINE, EMBASE and Cochrane databases.

Methods of study selection: Following PRISMA guidelines, in the last 20 years that reported on primary extra-pelvic endometriosis were included (PROSPERO registration number CRD42019125370).

Tabulation and integration: Initial search identified 5,465 studies and 179 studies, mostly case reports and series, were included. A total of 230 parietal (PE), 43 visceral (VE), 628 thoracic (TE), 6 central nerve system (CNS), 12 extra-pelvic muscle or nerves, and one nasal endometriosis papers were identified.

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Results: Abdominal endometriosis was divided into PE and VE. PE lesions involved primary lesions of the abdominal wall, groin and perineum where presenting symptoms were palpable mass (99%), cyclic pain (71%) and cyclic bleeding (48%). Pre-operative clinical suspicion was low and use of tissue diagnosis was indeterminate (25%), and a few (8%) malignancy suspected. Surgical treatment for PE included wide local excision (97%) with 5% recurrence and no complications. Patients with VE involving the abdominal organs – kidneys, liver, pancreas, biliary tract - were treated surgically (86%) with both conservative (51%) and radical resection (49%), with 15% recurrence and 2 major complications reported. In patients with TE involving the diaphragm, pleura and lung, isolated and concomitant lesions occurred and favored the right side (80%). Patients with TE presented with triad of catamenial pain, pneumothorax and hemoptysis. Thoracoscopic with resection followed by pleurodesis were the most

common procedures performed with 29% recurrence. Adjuvant medical therapy with GnRH was used in 15% of cases. Preoperative imaging with MRI was used in all cases of non-thoracic and non-abdominal endometriosis. Common symptoms were paresthesia and cyclic pain with radiation. Surgical resection was reported in 84% with improvement of symptoms.

Conclusions: Extra-pelvic endometriosis, traditionally thought to be rare, have been reported in a considerable number of cases. Heightened awareness and clinical suspicion of the disease, and multi-disciplinary approach is recommended to achieve prompt diagnosis and optimize patient outcomes. At this time, there are no comparative studies to provide recommendations regarding optimal diagnostic methods, treatment options and outcomes for endometriosis involving extra-pelvic sites.

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Keywords: Extra-pelvic endometriosis, parietal endometriosis, thoracic endometriosis, visceral endometriosis, lung endometriosis, nerve endometriosis, deep endometriosis

## Introduction

Endometriosis, defined as the presence of endometrial glands and stroma outside the uterine cavity, is a chronic inflammatory condition that causes pain and infertility in 10-15% of reproductive age women. (1). Deep endometriosis is differentiated from peritoneal (or superficial) and ovarian endometriosis types by the presence of endometriotic nodules larger than 5 mm (2). The most commonly accepted theory for the pathogenesis of endometriosis is retrograde menstruation where endometrial cells reach the abdomino-pelvic cavity via the fallopian tubes during menses, and depending on local and host immunologic factors, the ectopic endometrial cells go through neoangiogenesis, survive and implant (3). This theory is supported by the finding that the most frequently encountered sites of endometrial implants are located within the dependent aspects of the pelvis, such as the pouch of Douglas, retrocervix, uterosacral ligaments, rectosigmoid, and bladder (4).

Deep endometriosis has been found in extra-pelvic sites, such as the upper abdominal visceral organs, abdominal wall, diaphragm and pleura, perhaps as a result of peritoneal dissemination of endometrial implants and metaplasia (5). It also has been reported in even more distant sites, such as the central nervous system (brain, vertebral nerves) and the peripheral nervous system, perhaps by lymphatic or hematologic spread (6).

When extensive deep endometriosis involving distant sites and/or critical organs are encountered, the diagnosis and management of non-pelvic endometriosis can be extremely challenging and may result in delay in treatment. The main objective of this paper is to systematically review the literature to evaluate the clinical presentation, diagnostic methods, treatment modalities and outcomes of patients with extra-pelvic deep endometriosis.

## Methods

### *Search strategy*

A systematic review following PRISMA guidelines was performed (7). The review was registered in PROSPERO international prospective registry of systematic reviews in February 2019 (number CRD42019125370).

A literature search was performed using PubMed/Medline, Embase and Cochrane databases on February 12<sup>th</sup>, 2019. A combination of the following terms and its synonyms were utilized: extra-pelvic endometriosis, abdominal wall, diaphragm, pancreas, lung, pleura, blood vessels, groin, liver, central nervous system, nasolacrimal, lumbar spine, skeletal muscle, pericardium, kidney, cicatrix, scar, skin, endometriosis, endometrioma. The complete search strategy is illustrated in Figure 1.

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### *Selection Criteria*

Studies published in English, Spanish, Portuguese, French or Italian, in the last 20 years that reported on extra-pelvic endometriosis were included. To categorize the possible sites affected, studies were divided into the following: abdominal, thoracic and other (non-abdominal and non-thoracic) sites. Inclusion and exclusion criteria for each category are described in further detail below. Histological confirmation was required for inclusion of all cases, with exception of brain and heart endometriosis. Review articles and cancer-associated endometriosis studies were excluded. Definitions and specific selection criteria for each endometriosis category are provided below.

#### *Abdominal endometriosis*

Abdominal endometriosis is divided into two types, parietal endometriosis (PE) and visceral endometriosis (VE), for clarification in this systematic review. Parietal endometriosis include primary lesions that involve the abdominal wall, groin and

perineum. Exclusion criteria for PE of the abdomen include previous abdominal surgery and for PE of the perineum, vaginal deliveries with episiotomy/ laceration and/or vaginal surgeries. All reports (including single case reports) were included. Endometriosis lesions found in abdominal organs, such as the liver, pancreas, kidney and gallbladder are grouped under visceral endometriosis (VE). All studies on bowel endometriosis were also excluded as these are categorized as pelvic endometriosis.

#### *Thoracic endometriosis*

Thoracic endometriosis (TE) are endometriosis lesions that involve the diaphragm, pleura and lung (8). Thoracic endometriosis involving these three sites are grouped together because patients usually present with the same symptoms of catamenial pain or pneumothorax and hemoptysis (9). Due to the large number of single case reports and series of diaphragmatic and pleural endometriosis (total of 257) found in the literature search, case series with less than ten patients were excluded from this systematic review. All papers reporting on lesions involving the mediastinum (pericardium/heart) or lung parenchyma, however, were included given its rarity.

#### *Other sites of endometriosis*

All reports (including single case reports) of endometriosis involving vascular, lymphatic and the central nervous system, skeletal muscles, and peripheral nerves were included. Since brain endometriosis is extremely rare and obtaining brain biopsies carries significant risks, histological confirmation was not required for this particular site of endometriosis.

#### **Study selection**

Two reviewers (FVLA and CC) independently searched the literature. Conflicts regarding studies for inclusion were settled after discussion with a third author (MPA). Institutions, journals or authors were not concealed from the reviewers of this study.

### **Data extraction**

Data was abstracted into tables independently by three reviewers (FVLA, CC, LFCF and MPA), that included information on title, author's names, year of publication, type of publication, patients age, site of endometriosis, symptoms, surgical antecedents, coexistence of pelvic endometriosis, time to diagnosis, lesion size, imaging modality used for the diagnosis, treatment, and outcomes after treatment. Recurrence was defined by the original papers as recurrence of symptoms an/or recurrence of lesions by imaging.

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### **Risk of bias and Statistical Analysis**

Quality assessment was performed for all studies with more than ten patients by two reviewers (MPA and LFCF). Study Quality Assessment Tool was utilized according to the study design to assess the quality of observational studies (case series and case-control studies) (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>), while the Quality Assessment Tool for Diagnostic Accuracy (<https://www.bristol.ac.uk/population-health-sciences/projects/quadas>) was utilized for diagnostic accuracy studies. These questionnaires are composed by 9-14 questions regarding methodological quality of each included study. Based on such tools, authors critically appraised the included studies considering the risk for potential bias involving allocation, outcome measurement and confounding factors. Included studies were rated as "good" and "fair" quality, when there was a low risk of bias, and as "poor quality" when

there was a high risk of bias. Conflicts regarding study quality were resolved with the senior authors (RMK and MSA).

Data was abstracted from included studies and pooled as mean and standard deviation, median, absolute and relative frequencies.

## Results

### *Study Selection*

The initial search identified 5,465 studies, of which 1,092 from Medline, 4,333 from Embase and 40 from Cochrane database. After the review of the titles and abstracts, a total of 179 studies, were included for this systematic review (see Flow Diagram Figure 2). Except for one case-control studies that evaluated for accuracy of MRI for diaphragmatic endometriosis and two other case control studies on thoracic endometriosis, all other studies that fulfilled the selection criteria were case reports and series.

For abdominal endometriosis, a total of 126 studies were included, of which 88 (10-95) PE and 38 (96-133) VE. Among PE papers, 86 were single case reports and small case series (< 10 patients), and two were large case series (>10 patients). Among VE papers, 38 were single case reports and small case series. A total of 34 total studies (134-167) of thoracic endometriosis were included and involved patients with lesions involving diaphragm, pleura and/or lung, of which 31 were case series/case reports and 3 were case-control studies. Five studies that reported on pericardial endometriosis were excluded for not having complete clinical information or were submitted as surgical video papers.

For other (non-abdominal, non-thoracic) rare endometriosis sites, 19 studies (168-185) total were identified, all of which were single case reports.

### **Quality assessment**

Data regarding study quality is provided in Table 1. A total of 149 studies were single case reports and 15 were small case series. It should be noted that single case reports or small case series carry a major risk for bias including that of over-interpretation, inability to determine cause-effect, and lack of ability to make generalizations due to the small sample size.

The remaining 15 studies of larger case series and case control studies included were assessed according to the tools previously described. Of case series studies, 60% (9/15) were rated as good, 20% (3/15) were rated as fair and 20% (3/15) as poor quality (Table 1). The main risk of bias in these studies were inadequate length of follow up (32, 36, 136, 147) and no description of statistical analysis utilized (32, 36, 136, 138, 140, 142-145, 147). Both case-control studies (135, 186) had no sample size calculation, no blinded evaluators, and no adjustment of confounding variables. The one study assessing diagnostic accuracy (141) was considered of good quality. Minor limitations of this study included the indeterminate period of time between the standard and index test required to be reasonably sure that the target condition did not change, and the lack of blinded evaluators.

### **Abdominal Endometriosis**

Findings for abdominal endometriosis are reported below according to two categories, parietal endometriosis (PE) and visceral endometriosis (VE).

#### *Parietal Endometriosis*

A total of 88 studies that included 230 patients with primary PE were included in this systematic review. Of the 230 patients with PE, 133 were in the groin, 82 were umbilical, thirteen were in the abdominal wall, and two in the perineum. All cases were

primary lesions, that is, patients did not have any previous abdominal and perineal surgery or vaginal deliveries. Associated pelvic endometriosis was evaluated in a total of 134 patients with PE and was found in 18% (25/134) of them. In these cases with associated pelvic endometriosis, the PE lesions were not contiguous to the associated lesions found in the pelvis.

Median age of patients with PE at presentation was 38.5 (25-73) years. The most common clinical presentations were palpable mass (99%, 221/223), cyclic parietal pain (71%, 76/107), umbilical bleeding (48%, 38/78), and acyclic parietal pain (32%, 32/110).

Imaging modality was reported by 86 studies that involved a total of 120 patients. Of these studies, ultrasound was the most common (41%; 50/120) imaging modality utilized to diagnose PE, followed by magnetic resonance imaging (MRI) (18%; 22/120) and computed tomography (CT) scan (12%; 15/120) (Table 2). Of these, 37% (45/120) of patients (36 umbilical, 4 inguinal, 4 abdominal wall and 1 perineal endometriosis) were submitted directly to biopsy or excision without previous imaging exam, relying on clinical findings only. Two large case series with 110 total patients on inguinal endometriosis did not provide information on imaging exams used for diagnosis. Twelve cases of percutaneous fine needle aspiration (FNA) of the parietal lesions were reported of which 66.7% (8/12) confirmed endometriosis, 25% (3/12) were inconclusive and in 8.3% (1/12) malignancy was suspected. In thirty cases, tissue biopsies were performed preoperatively, mostly on cutaneous lesions, while one core biopsy was performed for an abdominal wall lesion, all of which confirmed diagnosis of primary PE. Only 39% (85/214) of patients had a preoperative diagnosis of endometriosis. The main initial diagnoses were groin/abdominal wall hernia (42%; n=90), unknown mass (5%; n=11), granuloma (1.4%; n=3), and melanoma (1.4%; n=3).

Only five case reports of umbilical endometriosis described the use of pre-operative medical treatment, one with combined oral contraceptive (COC), two oral

progestogens, and two with gonadotropin releasing hormone agonists (GnRHa).

Following medical treatment, improvement of symptoms was reported in 60% (3/5) of patients. In one case using oral progestogen, the lesion was reported to decrease in size and no surgical treatment was required.

Surgery was performed in 97% (222/227) of PE cases and was performed by general surgeons in 71.1% (158/222) of cases, gynecologists in 15.7% (35/222), dermatologists in 7.6% (17/222), and plastic surgeons in 3.1% (7/222). Procedures performed varied depending on the topography of the endometriosis lesion, but mostly involved wide local excision of the lesion (99%; 220/222). For umbilical lesions, omphalectomy and reconstruction of the umbilicus (36.9%; 82/222) was performed. Laparoscopic excision of two inguinal and one abdominal wall (transversus m.) endometriosis was reported in 0.9% (3/222) cases. Complete excision of PE lesion was accomplished in 99.3% (150/151) cases and no studies reported on any post-surgical complications.

Only ten cases reported the use of adjuvant hormonal treatment after surgical excision of which five used combined contraceptive, three GnRHa and two with progestins. Recurrences of PE lesions were described in 5% (7/135) of cases.

#### *Visceral Endometriosis (VE)*

A total of 43 patients with VE were included in this review (28 liver, 10 kidney, 3 pancreas, and 2 biliary tract) as shown in Table 2 (96-133). Median age of patients with VE was 40.3 (25-73) years. The most common presenting symptoms were upper abdominal pain (77%; 21/27) and abdominal mass (11%; 11/27) in patients with liver endometriosis; flank pain (60%; 6/10), hematuria (20%; 2/10), and pyelonephritis (20%; 2/10) in patients with kidney endometriosis; epigastric pain (100%; 3/3) and acute pancreatitis (33%; 1/3) in patients with pancreatic endometriosis; and acute liver failure

(50%; 1/2) and upper abdominal pain (50%; 1/2) in patients with liver endometriosis. Of all patients with VE, nine patients were postmenopausal, all of whom were with liver endometriosis. Of the nine postmenopausal patients, hormonal replacement therapy (HRT) use was reported in four, no HRT use in one, and no HRT information was available in the other four. In 32 of VE patients, previous or current pelvic endometriosis was investigated, and was reported in 62% (20/32) of them.

The most commonly used imaging modality for patients with VE was CT scan (72%; 31/43). Imaging findings were varied, comprising of simple and complex cystic lesions, and heterogeneous masses with and without contrast enhancement. Three percutaneous FNA biopsies were performed – two in kidney lesions suggesting endometriosis, and one in a liver lesion with unspecific results. Five percutaneous tissue biopsies were performed in liver lesions of which 80% confirmed endometriosis and 20% showed only necrotic tissue. Endometriosis was suspected based on clinical history and exams in 37% (11/29) of cases. Malignancy was suspected in 37% (11/29) of cases, and other (non-endometriosis) benign conditions were suspected in 24% (7/29) of cases.

Thirty-six studies with a total of 39 patients reported on hormonal treatment for VE. Hormonal treatment alone, that is, with no surgical treatment, with danazol (aromatase inhibitor) was reported in 7.6% (3/39) of VE cases. Two of these patients had liver endometriosis (lesion size ranged from 1-5 cm) and one kidney endometriosis. Although length of follow up was not reported, these patients had improvement of symptoms with danazol treatment. A case report of a patient with an 11 cm right lobe liver endometriosis showed no improvement of symptoms nor reduction of the size of lesion after the use of GnRHa for one year. This patient required subsequent surgery with hepatectomy.

Surgery was performed in 86% (37/43) of total cases. One asymptomatic 73 year old patient with liver endometriosis (that measured 7 cm) was followed conservatively,

without medications or surgery with no subsequent intervention required. Conservative surgery procedures for VE were performed in 51% (19/37) and included local resection (40%; 15/37), drainage (5.4%; 2/37) and partial nephrectomy (5.4%; 2/37), while a more radical procedure was performed in 49% (18/37), including partial hepatectomy (3.0%; 1/37) and complete nephrectomy (10.8%; 4/37; Table 2). Intraoperative frozen section was obtained in two cases that confirmed endometriosis of the liver and a conservative lesion resection alone was performed.

Post-surgical complications for patients with VE included one death caused by liver failure seven days after partial hepatectomy for a pre-operative suspicion of hepatocarcinoma in a 43 years old patient who presented acutely with dilated intrahepatic bile ducts; and one biliary leakage after hepatic cystectomy that resolved with conservative management. Of the 42 surgical cases, 38.0% (16/42) did not have recurrences, 15% (3/42) reported recurrences and in 54.7% (23/42) cases, information on recurrence was not reported. All 3 reported recurrences were in patients with liver endometriosis.

#### *Thoracic endometriosis*

Thoracic endometriosis (TE) was reported in 34 case series studies (134-167) that included a total of 628 patients (Table 3). Of these, 11 studies (495 patients) reported on diaphragmatic endometriosis, 5 studies (90 patients) on pleural, and 21 studies (28 patients) on lung endometriosis. In 1,11% (7/628) patients, concomitant diaphragmatic, pleural and lung involvement was observed, while an isolated lesion on the diaphragm was noted in 44.5% (280/628) of patients, on the pleura in 12.7% (80/628) and in 4.5% (28/628) patients on the lung. Overall, the median age at presentation for patients TE was 22.6 (16-54) years. In all patients, diagnosis was confirmed with histology preoperatively by the presence of endometrial glands or stroma

or immunohistochemistry with positive nuclear staining for either estrogen or progesterone receptors. In six included studies (n=318), smoking history was evaluated because of the respiratory symptoms reported upon clinical presentation. There was no history of tobacco use in 73.8% (235/318) of patients with TE. Smoking regularly was reported in 14% (40/318) of patients.

Pneumothorax was the most common presenting symptom (69.9%; 439/628) in TE cases. TE was right sided in 80% of cases. The mean number of episodes of pneumothorax was  $3.1 \pm 2.7$ . The association of TE and pelvic endometriosis was found in 52.9% (186/351) women from 13 studies and the diagnosis of pelvic endometriosis was made through characteristic findings from imaging or pelvic surgery.

The most common initial imaging exam used was chest x-ray (31%; 189/600) to evaluate patients who present with pneumothorax episodes. Chest CT was performed in 14.3% (90/628) of cases. There were no studies evaluating the accuracy of imaging methods for the evaluation of overall TE lesions.

#### *Diaphragmatic and pleural endometriosis*

Diaphragmatic endometriosis was reported in 11 identified studies with a total of 495 patients (Table 3). In these patients, catamenial pneumothorax was the most frequent symptom reported (41%; 202/495), followed by non-catamenial pneumothorax (25%; 123/495) and catamenial chest pain (10%; 49/495) with scapular or cervical radiation due to the phrenic nerve involvement.

One study with 33 patients with diaphragmatic endometriosis evaluated the accuracy of MRI for these lesions. This study reported a sensitivity of 83% for MRI, when using a fat-suppressed T1-weighted sequences for the diagnosis of diaphragmatic endometriosis.

Five studies reported on a total of 90 patients with pleural involvement. Main symptoms in patients with pleural endometriosis were catamenial pneumothorax in 61% (55/90), catamenial chest pain 23% (20/90) and hemoptysis in 1% (1/90).

The surgical approach of choice for the treatment of diaphragm and/or pleural endometriosis was video-assisted thoracoscopic surgery (VATS) in 12 of 13 studies (72%, 443/615). The main surgical VATS finding was a diaphragmatic defect, often with visualization of the liver through the defect.

Three studies reported the need for a thoracotomy for patients who have had a previous thoracotomy or with complex diaphragmatic lesions (that is, when the diaphragmatic lesions were proximal to the phrenic nerve or its main branches, or when their number, size and / or location prohibited an endoscopic resection) (144). In these studies, thoracotomy, as opposed to an endoscopic approach was preferred in order to avoid important adjacent structures, such as the phrenic nerve, superior vena cava or pericardium. In eight studies (n=151) pleural lesions were resected by pleurectomy or partial resection of lung parenchyma, followed by pleurodesis in all cases. Surgical treatment of diaphragmatic lesions, reported in 370 patients, included coagulation of superficial endometriotic implants (27.2%; 101/370), and partial diaphragm resection and suturing (78.1%; 289/370) for deep lesions. Adjuvant hormonal therapy with GnRHa was prescribed routinely after surgical treatment in 15.5% (77/370) patients.

The follow up time for patients with pleural or diaphragmatic endometriosis ranged from 3 to 168 months in 10 studies (total of 478 patients). Recurrence of pneumothorax after surgical treatment was reported in 29.0% (139/478) cases of pleural/diaphragm endometriosis.

*Lung endometriosis*

Twenty-one studies reported on lung endometriosis with a total of 28 patients (Table 3). Median age of patients at presentation was 34.1(19-54) years. The main presenting symptom reported was catamenial hemoptysis (82.1%; 23/28), followed by cough (14.3%; 4/28), and pneumothorax (14.3%; 4/28). Dyspnea was reported by only 7.1% (2/28) of women with pulmonary endometriosis.

The most common initial exam performed for lung endometriosis was chest x-ray (39%; 11/28). Chest CT scan during menses was obtained and confirmed the presence and location of the parenchymal endometriotic lesion in 89% (25/28) of patients.

Lung endometriosis lesions were right sided in 62.5% (15/24), left sided in 29.0% (7/24) and bilateral in 8.3% (2/24) of cases. In 67% (19/28) of patients with lung endometriosis, bronchoscopy was performed and in only two patients, bronchial washing was performed and revealed endometrial cells.

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Surgical treatment was performed in 82.1% (23/28) cases of pulmonary endometriosis. In 10.7% of cases, no surgery was performed and patients were referred for exclusive medical therapy with GnRHa. Most of the surgical procedures (59.0%; 13/22) were performed through video assisted thoracoscopy (VATS). They included pulmonary parenchymal resection associated with pleurodesis (73.9%; 17/23), lobectomy (21.7%; 5/23), and pleural resection (4.3%; 1/22). In 18.1% (4/22), information on surgical procedure was not provided. Additional pleural abnormalities such as red and brown pleural endometriotic lesions were ablated during surgery.

In three cases (10.7%; 3/28), patients were treated only with hormonal treatment with GnRHa. Three studies (involving three patients) did not provide any information regarding the use of preoperative nor adjuvant medical treatment. There were no recurrences after surgical or medical treatment during the median follow-up of 22.6 months (range: 4 to 60 months) in nine studies that involved 31 patients.

*Other sites of extra-pelvic endometriosis*

A total of 19 studies reported on 19 single cases of non-abdominal and non-thoracic sites of endometriosis (Table 4). These rare sites included six cases involving the central nervous system (one on brain, one on lumbar vertebra, and four on the conus medullaris), twelve patients with extra-pelvic muscles and peripheral nerves, and one case of nasal endometriosis. Patients age ranged from 21 to 58 years.

In all cases of central nervous (n=6) and extra-pelvic muscles and peripheral nerve (n=12) endometriosis, patients presented with paresthesia and cyclic pain with radiation according to the topographic site involvement. In 38.8% (7/18) cases, patients also presented with severe dysmenorrhea. In one case of brain endometriosis, symptoms of cyclic seizures, cyclic hemiparesthesia and cyclic headache were reported. In endometriosis affecting the conus medullaris (n=4), patients also presented with urinary retention and bowel dysfunction.

MRI was utilized in all cases of extra-pelvic endometriosis, which showed a hyperintense T1 or isointense T2 lesion. The mean size of these lesions were  $1.6 \pm 1.3$  cm (reported in 2/6 cases) and  $4.5 \pm 3.1$  cm (reported in 10/12 cases), respectively.

In 83.3% (5/6) of central nerve endometriosis, surgical excision was the definitive treatment with complete resolution of symptoms. In four of these patients, complete resolution of symptoms was achieved and in one case of conus medullaris endometriosis who presented preoperatively with motor impairment of lower limbs and bladder and intestinal dysfunction, symptoms improved partially after surgery. The patient with brain endometriosis was treated exclusively with GnRHa and bilateral salpingo-oophorectomy with complete resolution of symptoms. Adjuvant hormonal treatment, with GnRHa (33.3%; 2/6) and danazol (66.6%; 4/6), was used in all cases of central nervous endometriosis.

Surgical excision was the definitive treatment in 91% (11/12) of muscular and peripheral nerve endometriosis cases, with complete and partial improvement of symptoms in 90.9% (10/11) and 9% (1/11), respectively. In one case of endometriosis affecting the gluteal muscle and nerve, the patient presented preoperatively with motor dysfunction that did not improve after surgery. Adjuvant hormonal therapy after muscular/ peripheral nerve endometriosis resection was reported in 33.3% (4/12) cases, with GnRHa in three cases and combined contraceptive in one case. One patient with extra-pelvic sciatic endometriosis was treated exclusively with GnRHa with complete resolution of symptoms. Follow up time reported in five cases was 6-72 months with no recurrences noted.

One study reported on a rare case of nasal endometriosis in a 35 year-old patient who presented with cyclic epistaxis. Nasal endoscopy with biopsy confirmed endometriosis. Patient was treated with medical treatment (GnRHa) with complete resolution of symptoms after a follow up of 5 years.

## Discussion

Primary extra-pelvic endometriosis can affect nearly every organ system of the female body (Figure 3). This systematic review revealed that extra-pelvic and distant disease, historically considered to be rare, have been reported by a considerable number of studies such that the incidence may not be that rare after all. The collection of data from the case reports and series provides cumulative insight but precludes us from making conclusive statements regarding incidence or cause-effect. This study is also limited by the lack of comparison analysis data available regarding diagnostic tools, medical and surgical treatment outcomes for these lesions. Aware of these limitations, we provide here a synthesis of the cumulative data obtained from the identified studies

in order to gain greater understanding of the different extra-pelvic sites of involvement, various clinical presentation, pre-operative diagnostic methods, treatment options and outcomes of patients with this challenging disease.

*Sites of involvement.* Because of its extra-pelvic location, clinical suspicion for endometriosis was reportedly low (39%) and most patients were treated by non-gynecologic providers (84%). Abdominal and thoracic endometriosis, specifically inguinal, umbilical and diaphragmatic endometriosis, accounted for most of the cases identified in this review. In the general surgery literature, 7.3% of female patients who underwent inguinal hernia surgery were noted to have inguinal endometriosis (36). The umbilicus, abdominal wall muscles, and the perineum also can be affected with primary PE. Compared to PE, fewer cases of VE were reported involving different abdominal organs- liver, kidney, and pancreas, and where a large proportion of VE patients had concomitant pelvic endometriosis was noted (62%). A thorough pelvic survey should therefore be performed when a patient with VE is encountered.

Thoracic endometriosis is reported to occur more frequently as an isolated diaphragm lesion, followed by pleural lesion and lung. In most cases of TE, lesions involving the diaphragm, pleura and lung coexist and reflect the multiple observed presentations of thoracic endometriosis syndrome (described below). A majority (80%) of TE was noted to favor the right side which may support the previously proposed theory that endometriosis travels from the peritoneal cavity to the chest via diaphragmatic defects, implanting in the pleural surface and adjacent lung (155, 187).

Malignancy represented the most common (37%; 11/29) differential diagnosis in many of the reported VE cases. Knowing that overtreatment for an erroneous diagnosis can be fatal (96), awareness of the various possible sites for endometriosis could heighten the clinical suspicion so that delay in diagnosis can be avoided and proper treatment hastily provided.

*Clinical presentation.* Patients with extra-pelvic endometriosis in the abdomen, thoracic and distant sites were predominantly of reproductive ages, specifically in the 30's-40's age range. Less frequently, cases of menopausal women were reported, primarily with visceral (nine patients with liver endometriosis) and extra-pelvic musclicutaneous involvement (one patient with dorsal skin endometriosis). Clinical presentation varied depending on the topographical site of involvement - mass, cyclic bleeding and pain for abdominal endometriosis; pneumothorax and chest pain for thoracic; cyclic muscle pain and neurological symptoms for patients with muscular and nerve involvement.

The diagnosis of TE is difficult and depends heavily on clinical suspicion (188). Patients with suggestive symptoms or proven pelvic endometriosis with chest complaints should alert the gynecologist to possible thoracic involvement. Thoracic endometriosis syndrome (TES) has been described that involves several, sometimes overlapping, clinical presentations (144). From this systematic review, the main symptoms were, in order of frequency, catamenial pneumothorax, non-catamenial pneumothorax, catamenial chest pain, pleural effusion, hemothorax and catamenial hemoptysis. "Catamenial" for all symptoms was defined as occurring from 24 hours before to 72 hours after the onset of menstruation. Although most symptoms are unequivocally catamenial, non-catamenial manifestations are also possible, either when the natural course of disease evolves toward a progressive clinical deterioration - chest pain persisting for many months - or when remarkable anatomic alterations occur, as in the case of diaphragmatic hernia (135).

*Pre-operative imaging methods and tissue diagnosis.* Ultrasound appears to be the more commonly used modality for superficial (cutaneous, abdominal) lesions while CT scans or MRI were utilized for intra-abdominal and difficult to access lesions. When patients with TE present with pneumothorax, chest x-ray was the most commonly used

imaging modality for evaluation followed by chest CT. Radiologic findings in patients with TE varied to reveal pneumothorax, pleural effusions, nodules, opacities and nodular infiltrates, thin-walled cavities, segmental atelectasis, or bullous formation (189). Based on one study, the use of MRI imaging for the diagnosis of endometriosis of the diaphragm has a sensitivity of 83%. MRI findings of diaphragmatic lesions can vary from punctate spots and plaques to deep nodules, better depicted on fat-suppressed T1-weighted sequences (141). As there were no comparative studies identified that compared different imaging modalities, we are unable to determine which imaging tool is optimal for abdominal or thoracic endometriosis disease.

While the suspicion for endometriosis was made based primarily on clinical history and exam alone, in some cases, malignancy was suspected that may have led to a more aggressive surgical procedure. Percutaneous biopsies, FNA and frozen section during surgery could be options to prevent overtreatment. However, in many cases, the use of fine needle aspiration nor tissue biopsies were non-confirmatory for endometriosis. The classic "triad" of endometrial glands, stroma and hemosiderin-laden macrophages were identified in only one third of surgical specimens. The use of immunohistochemistry, using antibodies against ER, PR and CD10, has therefore been proposed to be helpful when endometrial glands are not present in the tissue sample or when only a small foci of endometrial stroma is found (137). For VE cases, the use of intra-operative frozen section may allow for confirmation of a benign process of endometriosis - as opposed to cancer - and a subsequent conservative procedure is performed, rather than a radical resection with complete loss of organ.

*Treatment options and outcomes.* When endometriosis was confirmed with pre-operative tissue diagnosis, observant management alone without medical or surgical treatment has been reported in asymptomatic patients. In most other cases, surgery was indicated to obtain and confirm the diagnosis. With the limited evidence, we are unable

to determine the best treatment choice for each type and extent of extra-pelvic endometriosis. For most cases, however, surgical treatment was performed and varied from ablation, partial or complete resection, or bilateral oophorectomies. Surgery with complete excision for superficial lesions of PE was performed in 97% of reported cases with no reported subsequent complications and low recurrence rates (5 and 15%) (99-101, 107, 109, 112, 115, 116, 125, 128, 129). In contrast to patients with PE, major complications (including biliary leak and death) and recurrences are reported in patients with VE (96, 126).

Treatment of TE is predominantly surgical, due to the high failure rate of isolated hormonal therapy. Conservative focal resections and repair of pleural and diaphragmatic defects through thoracoscopy, combined with or without laparoscopy, were the surgical principles advocated. Because recurrence of pleural/diaphragm endometriosis after surgical resection was reported in up to a third of surgical cases, we recommend that adjuvant hormonal therapy and/or continued close surveillance of these patients should be considered.

In severe cases of extra-pelvic endometriosis where surgical resection was deemed to incur significant risks, the use of GnRH agonist with bilateral oophorectomies had been successful in achieving complete resolution of symptoms such as in extra-pelvic sciatic nerve, brain and intra-nasal endometriosis. For neural involvement, persistent long term motor/sensory impairment have been reported after surgical excision.

## **Conclusion**

The large body of case reports and series identified in this systematic review reveals that extra-pelvic endometriosis may not be that rare after all. However, evidence-based approach to the diagnosis and treatment of affected patients remains enigmatic given its low prevalence and the limited quality of studies available in the literature. The

development of a worldwide registry of patients with extra-pelvic endometriosis from multiple high volume centers may overcome these limitations. Detailed reporting of cases with clearly defined data points and validated patient assessment tools would be helpful. For now, the prompt diagnosis and proper treatment of extra-pelvic endometriosis requires a heightened level of awareness of this disease entity. Also, as patients often present initially to non-gynecologic services, multi-disciplinary collaboration and approach is critical in order to optimize patient outcomes.

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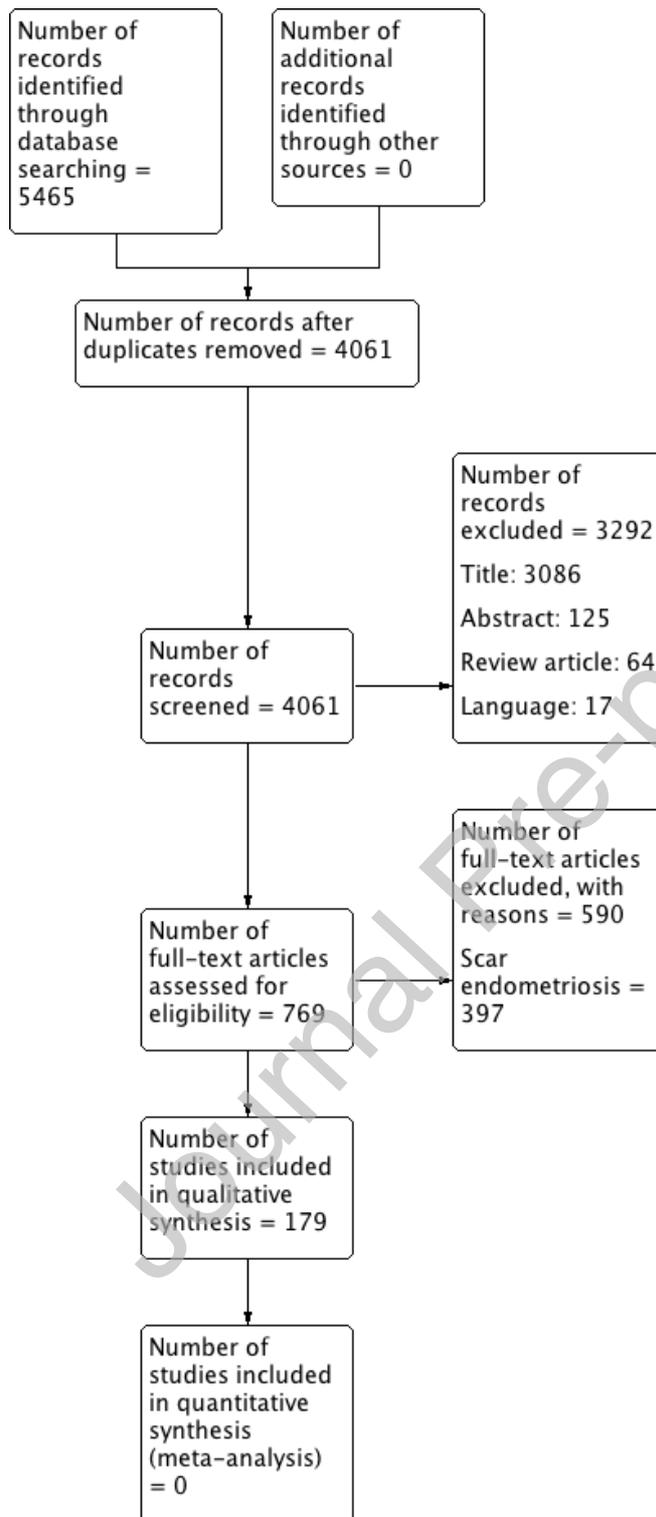
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## Figure's legend

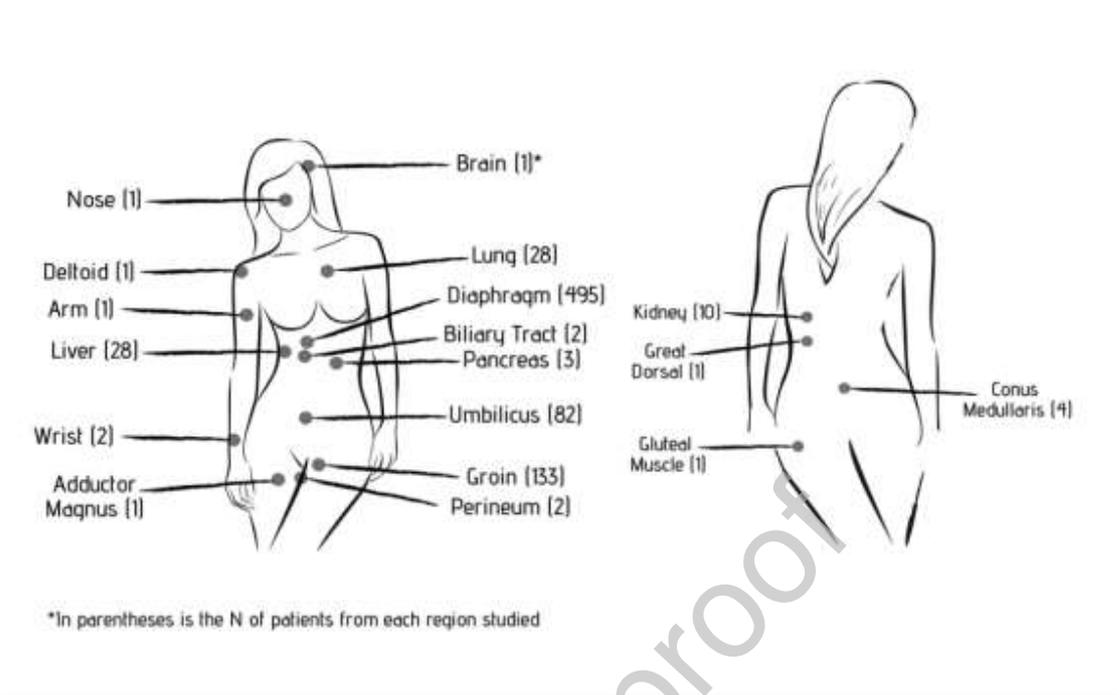
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## Figure 1 – Search strategy



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Figure 2 – Flowchart of systematic review on extra-pelvic endometriosis



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**Figure 3- Extra-pelvic reported sites of endometriosis**

**Table's legend****Table 1 – Quality assessment of case series, case-control and accuracy studies included in this systematic review**

Numbers refers to each question of quality assessment questionnaires. Study Quality Assessment Tool was utilized according to the study design to assess the quality of observational studies (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>) while the Quality Assessment Tool for Diagnostic Accuracy (<https://www.bristol.ac.uk/population-health-sciences/projects/quadas>).

Y: yes; N: no; CD: cannot determine; NA: not applicable; NR: not reported

**Table 2 – Studies on abdominal endometriosis**

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<sup>a</sup>Rectus abdominis muscle (4 cases), Subcutaneous tissue (2 cases), Transversalis muscle (1 case), Pyramidalis muscle (1 case), Pre peritoneal fat (1 case), Unspecified (3 cases).

<sup>b</sup>Gallbladder (one case) and extra-hepatic bile duct (one case). FNA: fine needle aspiration; MRI: Magnetic Resonance imaging; CT: Computed Tomography; COC: combined oral contraceptive; GnRHa: Gonadotropin Releasing Hormone Agonist

**Table 3 – Studies on thoracic endometriosis**

VATS: Thoracoscopy, MRI: Magnetic Resonance Imaging; CT: Computed Tomography, GnRHa: Gonadotropin Releasing Hormone Agonists; NR: not reported

\*These lesions can occur simultaneously in the same patient

**Table 4 - Studies on non-abdominal rare sites of endometriosis**

GnRHa: Gonadotrophin releasing agonist; BSO: bilateral salpingoophorectomy; <sup>a</sup>Sites involved by endometriosis: Deltoid muscle (1), Dorsal skin (1), Gluteal (2), Obturator internus muscle and nerve (1), Piriform muscle (1), Adductor magnus muscle (1), Arm (1), Wrist (1), Gastrocnemius (1).

Table 1 – Quality assessment of case series, case-control and accuracy studies included in this systematic review

Lead author, year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Study Design	Quality
<i>Rousset P, 2016</i>	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Diagnostic accuracy	good
<i>Fukuoka M, 2015</i>	Y	Y	N	Y	Y	Y	NA	N	Y	Y	N	N	-	-	Case control	fair
<i>Haga T, 2015</i>	Y	Y	N	Y	Y	Y	NA	N	Y	Y	N	N	-	-	Case control	fair
<i>Mourra N, 2015</i>	Y	Y	Y	Y	Y	Y	N	N	Y	-	-	-	-	-	Case series	good
<i>Kurihara M, 2014</i>	Y	N	NR	NR	Y	Y	N	N	N	-	-	-	-	-	Case series	poor
<i>Kawaguchi Y, 2018</i>	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	-	-	-	-	Case series	good
<i>Bobbio A, 2017</i>	Y	Y	Y	Y	Y	Y	Y	N	Y	-	-	-	-	-	Case series	good
<i>Brandolini J, 2010</i>	Y	Y	Y	Y	Y	Y	Y	N	N	-	-	-	-	-	Case series	good
<i>Ouede R, 2018</i>	Y	Y	Y	Y	Y	N	Y	N	Y	-	-	-	-	-	Case series	good
<i>Ghina M, 2015</i>	Y	Y	Y	Y	Y	Y	Y	N	Y	-	-	-	-	-	Case series	good
<i>Alifano, 2007</i>	Y	Y	Y	Y	Y	Y	Y	N	Y	-	-	-	-	-	Case series	good
<i>Bobek V, 2017</i>	Y	N	NR	NR	Y	N	NA	N	N	-	-	-	-	-	Case series	poor
<i>Bagan P, 2003</i>	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	-	-	-	-	Case series	good
<i>Bubak J, 2017</i>	Y	Y	Y	Y	Y	Y	Y	N	N	-	-	-	-	-	Case	fair

Miyazaki K,  
2017

series  
Case series poor

Numbers refers to each question of quality assessment questionnaires. Study Quality Assessment Tool was utilized according to the study design to assess the quality of observational studies (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>) while the Quality Assessment Tool for Diagnostic Accuracy (<https://www.bristol.ac.uk/population-health-sciences/projects/quadas>).

Y: yes; N: no; CD: cannot determine; NA: not applicable; NR: not reported.

Table 2 – Studies on abdominal endometriosis

Site	Studies	N	Age (median)	Symptoms	Preoperative evaluation	Treatment Options
<b>Parietal</b>						
Umbilicus	59	82	37.8±6.8	Palpable Mass (221/223) Cyclic Pain (76/107) Acyclic Pain (36/110)	US (50/120) MRI (22/120) CT (15/120)	Surgery (222/230) Complete excision (150/151) Recurrence of lesion (7/135)
Groin	14	133	37.2	Umbilical Skin Lesion (63/70) Umbilical bleeding (38/78)	Imaging not reported (110/230)	Adjuvant medical treatment (10/230) COC (5) Progesterogens (2) GnRH (3)
Abdominal Wall <sup>a</sup>	13	13	32.5±5.7		FNA (12/230) Tissue biopsy (30/230)	Medical treatment (5/230) COC (1) Progesterogens (2) GnRHa (2)
Perineum	2	2	28±1.4			Symptom improvement (3/5) Lesion decrease (1/5)
Total	88	230	38.5 (25-73)			
<b>Visceral</b>						
Liver	23	28	39.9 (25-73)	Upper abdominal pain (21/27) Abdominal mass (11/27) Consumptive syndrome (1/27) Shoulder pain (1/27) Imaging Finding (1/27)	CT (31/39) MRI (17/42) US (13/37) FNA (3/41) Tissue biopsy (5/42)	Surgery (37/43) Type of surgery Lesion resection (15) Partial hepatectomy (11) Nephrectomy (4) Partial nephrectomy (2) Distal pancreatectomy + splenectomy (2) Cyst drainage + biopsy (2) Cholecystectomy (1)
Kidney	10	10	41.4 (35-53)	Local pain (6/10) Hematuria (2/10) Pyelonephritis (2/10) Incidental Finding (2/10)		Complications Death after partial hepatectomy (1) Bile leakage after hepatic cystectomy (1) treated conservatively for 6 weeks
Pancreas	3	3	40.3 (35-43)	Epigastric pain (3/3) Acute pancreatitis (1/3)		Symptom improvement (43/43).

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Biliary tract <sup>b</sup>	2	2	40.3 (43-55)	Acute liver disease (1/2) Upper abdominal pain (1/2)	Hormonal treatment (4/39) Danazol (3) - no follow up, no surgery GnRHa (1) – persistent symptom proceeded to surgery
					No treatment: 1 asymptomatic liver cyst
Total	38	43	40.3 (25-73)		

<sup>a</sup>Rectus abdominis muscle (4 cases), Subcutaneous tissue (2 cases), Transversalis muscle (1 case), Pyramidalis muscle (1 case), Pre peritoneal fat (1 case), Unspecified (3 cases). <sup>b</sup>Gallbladder (one case) and extra-hepatic bile duct (one case). FNA: fine needle aspiration; MRI: Magnetic Resonance imaging; CT: Computed Tomography; COC: combined oral contraceptive; GnRHa: Gonadotropin Releasing Hormone Agonist

Table 3 – Studies on thoracic endometriosis

Site	Studies	n	Age (median)	Symptoms	Preoperative evaluation	Treatment Options
<b>Thoracic endometriosis (total)</b>	24	628	22.6 (16-54)	Pneumothorax (70%) Right sided (80%) Pelvic endometriosis (53%)	Chest CT (16%) Chest X-ray (31%)	
Diaphragm	11*	495	35.0±3.1	Catamenial Pneumothorax (41%) Chest Pain (10%) Non- catamenial Pneumothorax (25%) Scapular pain (10%)	Diaphragm MRI (fat-suppressed T1-sequences) 33 patients: sensitivity 83%	Surgical treatment (370/495) Suture of diaphragm holes/ Partial resection (289) Stripping or coagulation of lesions (101) Adjuvant GnRHa (289)
Pleural	5*	90	25.5 (19-52)	Catamenial Pneumothorax (61%) Chest Pain (23%) Hemoptysis (1%)		Surgical treatment (NR) Pleural abrasion Adjuvant hormonal suppression with GnRHa or cyproterone
Lung	21	28	34.1(19-54)	Catamenial hemoptysis (82%) Cough (14%) Pneumothorax (14%) Dyspnea (7%)	CT in menses (89%) Bronchoscopy (67%) Chest X ray (39%)	Surgical treatment (23/28) Parenchima resection (17) Lobectomy (5) Pleural resection (1)  Hormonal treatment (4/28) GnRHa only (3)

VATS: Thoracoscopy, MRI: Magnetic Resonance Imaging; CT: Computed Tomography, GnRHa: Gonadotropin Releasing Hormone Agonists; NR: not reported

\*These lesions can occur simultaneously in the same patient

Table 4- Studies on non-abdominal rare sites of endometriosis

Site	Studies	N	Age (median)	Symptoms	Preoperative evaluation	Treatment Options
<b>Central Nervous System</b>						
Brain	1	1	41	Seizures, Hemiparesis, Headache, Dysmenorrhea	MRI (hyperintense T1/ isointense T2 lesion)	GnRHa + BSO with complete resolution of symptoms
Conus medullaris	4	4	30.8 (25-40)	Paresthesia (4/4), Lumbar pain (4/4), Urinary/bowel dysfunction (4/4), Dysmenorrhea (4/4)	MRI (hyperintense T1/ isointense T2 lesion)	Surgical resection with partial (1/4)/ complete (3/4) resolution of symptoms Adjuvant hormonal treatment GnRHa (1) Danazol (3)
Lumbar vertebra	1	1	33	Lumbar pain (1/1), Dysmenorrhea (1/1)	MRI (hyperintense T1/ isointense T2 lesion)	Surgical resection + adjuvant Danazol with complete resolution of symptoms
<b>Muscles/nerves</b>						
Soft tissue/ nerves <sup>a</sup>	10	10	32.6 (21-58)	Swelling (1/1), Cyclic pain (1/1)	MRI	Surgical resection with improvement of pain symptoms in all cases. One patient (gluteal lesion) had a permanent muscular functional impairment Adjuvant hormonal treatment GnRHa (1) Combined contraceptive (1) No hormonal treatment (1) Not reported (7)
Extrapelvic sciatic nerve	2	2	36.0 (36-39)	Gluteal pain radiating to the right dorsal thigh (2/2)	MRI	Surgical excision + adjuvant GnRHa (1/2) with complete resolution GnRHa only (1/2) with complete resolution
<b>Other sites</b>						
Nasal	1	1	35	Cyclic epistaxis, Nasal pain, Dysmenorrhea (1/1)	Nasal endoscopy	GnRHa with complete resolution

GnRHa: Gonadotrophin releasing agonist; BSO: bilateral salpingoophorectomy; <sup>a</sup>Sites involved by endometriosis: Deltoid muscle (1), Dorsal skin (1), Gluteal (2), Obturator internus muscle and nerve (1), Piriform muscle (1), Adductor magnus muscle (1), Arm (1), Wrist (1), Gastrocnemius (1).