Catamenial pneumothorax

Is it time to approach differently?

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ABSTRACT

Catamenial pneumothorax (CP) was considered a rare clinical entity that has gained tremendous interest recently. It is commonly overlooked, misdiagnosed, or under diagnosed. It is part of the thoracic endometriosis syndrome, which includes catamenial hemothorax, catamenial hemoptysis, and pulmonary endometriosis. These represent the spectrum of ectopic pelvic endometriosis. The presentation is variable leading to difficulty in developing a standardized approach to diagnosis and management. This review discusses the pathogenesis of these entities and the novel methods of investigation, management, and clinical protocols.


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The scope of thoracic pathologies encountered in clinical practice has changed since the early days of Hippocrates, where empyemas and infective cases were the dominating majority. The significant shift seen in recent years is in the field of thoracic oncology, mainly lung and esophageal cancers. This has been driven by improved access to health care systems and advances in diagnostic technology. Importantly, other benign and rare thoracic pathologies deserve such “physician-awareness and updates” to be able to identify and effectively explore treatment options to date. Such pathologies were considered rare but with such awareness it has been proven otherwise. Thoracic endometriosis syndrome (TES) and in particular the catamenial pneumothorax (CP) are among these pathologies. Recent literature increasingly reports these entities and demonstrates a shift in understanding and management. The presence of ectopic endometrial tissues in the thoracic cavity is defined as TES. This includes lesions in the diaphragm, pleura, lung parenchyma, or the airways. The mode of presentation is variable and includes sub-entities. It was considered a diagnosis of exclusion but recent advancement in its investigation allowed clinicians to establish diagnostic thresholds and to implement better management protocols. In this review, CP will be reviewed discussing its history, pathological definitions, etiological theories, and epidemiology. Aspects from clinical presentations to investigation and management options as well as controversies will be discussed.

Endometriosis. Endometriosis is the presence of endometrial tissues outside the uterine cavity. They are mainly found in the pelvis and peritoneal surfaces such as the serosal surface of the uterus, rectovaginal septum, sigmoid colon, or small intestine. Extra-pelvic endometriosis (EPE) is located in 4 anatomical regions: pulmonary endometriosis, bowel-omental endometriosis, urinary tract endometriosis, and other locations. The presence of EPE has been reported in locations such as the umbilicus, abdominal scars, breast, extremities, and in the thorax. The most common
location for EPE is in the thorax. It is common in women in the reproductive age, with the mean age of presentation being 34 years (range 15-45 years). It is also commonly seen in nulliparous females. It is estimated to occur in 5-15% of primary spontaneous pneumothoraces in females. It is a chronic condition presenting with a range of symptoms including chronic pelvic pain, infertility, dyspareunia, non-cyclic abdominal pain, dysfunctional uterine bleeding, or dysmenorrhea. The symptoms of EPE depend on the location and the organ involved. It is usually related to the menstrual cycle. The true prevalence of EPE is lacking.

**Thoracic endometriosis syndrome (TES).** The first described clinical syndrome associated with menstruation was in 1885 by Gowens where he described seizure activities coinciding with the menstrual cycle. Schwarz reported endometriosis of the lung parenchyma in 1938. Recurrent pneumothorax associated with menstruation was reported by Mauer in 1958. Such clinical associations entertained the retrograde menstruation theory described by Schron and Ruysch almost 240 years ago. Therefore, the hypothesis behind it at that time was endometrial auto-transplantation to other sites possibly by lymphatic, vascular, or other routes. The syndrome has a variety of clinical and radiological manifestations depending on implants within the thoracic cavity. These implants slough during the menstrual cycle and cause a spectrum of presentations ranging from CP (73%), catamenial hemotorax (14%), catamenial hemoptysis (7%), endometrial nodules (6%), as well as catamenial pneumodiastinum, and isolated chest pain. Interestingly, TES is right-sided in 85-90% of cases. There is an average lag time to diagnosis of about 5 years. There is not a general agreement on the time frame, some claim that CP coincides with menstruation in the absence of lung disease and others believe it occurs within 72 hours before or after menstruation.

**Theories.** Over the years, several theories have emerged to describe the pathogenesis. Each of these is based on either an embryological principle or a correlation with an anatomical or clinical observation. Some overlap exists among these theories.

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**Coelomic metaplasia theory.** Also called Müllerian theory or Ivanoff metaplasia theory is based on the notion that endometrial, pleural, and peritoneal mesothelium share the same origin, namely undifferentiated peritoneal cells. Therefore, any pathological stimulus that can activate precursor cells in these sites will result in coelomic metaplasia and the development of CP. One of the shortcomings of this theory is that it cannot explain the right side dominance and the occasional presence of an inter-parenchymal nodule.

**Embolization theory.** Also known as lymphatic-hematogenous embolization theory, metastatic embolization, or lymphatic-hematogenous transplant theory, embolization theory explains the routes where endometrial implants reach the thorax through lymph channels or blood vessels. Supporting this theory is the observation of an increased incidence after trauma and gynecological manipulation that might predispose to microembolization. Moreover, in autopsies, bilateral inter-parenchymal nodules were found in some cases.

**Retrograde menstruation theory.** Also called Sampson’s theory or migration theory, retrograde menstruation theory entails the successive steps of retrograde menstruation with endometrial tissues traveling within the peritoneal fluid circulation followed by the trans-diaphragmatic passage to the thorax. The peritoneal circulation has a preferential flow clockwise towards the right paracolic gutter reaching the right sub-phrenic area. At this point, the liver dampens the flow redirecting the fluids including the implants through the diaphragmatic pores. This process could be augmented at times where there is increased intra-abdominal pressure.

**Intraperitoneal air theory.** Also called the lack of cervical mucus plug theory, intraperitoneal air theory posits that air passes under atmospheric pressure through the uterus via the cervix. Usually this is prevented by the presence of the mucus plug, but this could be lacking in susceptible patients, likely due to hormonal disturbances. Once in the uterus, air travels in retrograde fashion through the fallopian tubes into the peritoneal cavity. Uterine contractions, physical efforts, or other activities push the air to the peritoneal cavity. As a prerequisite, diaphragmatic pores have to be present for the air to pass to the thorax trans-diaphragmatically. This theory is supported by the observation that there is a simultaneous presence of pneumoperitonium and pneumothorax. Also in support of this theory are the reported cases of pneumothorax after knee-chest exercise, postpartum spontaneous pneumothorax, vaginal douching, and postcoital pneumothorax. Moreover, a decrease in the rate of recurrence and even cure were reported after tubal ligation.
Rossi and Goplerud’s theory. Also called prostaglandin F2alpha theory, this theory is based on the increased levels of prostaglandin F2alpha during menstruation and the subsequent broncho-vascular spasm leading to localized increased pressure and pleural rupture. The check-valve mechanism is precipitated by the response of endometrial implants within the parenchyma and airways to prostaglandin F2alpha and subsequently swelling of these implants results in hyperinflation and pneumothorax. This theory can explain CP in the absence of diaphragmatic pores. The presence of pleural adhesions can create a state of increased pressure that might act as a barotrauma and subsequent pneumothorax.

The theory of Kirschner. This concept addresses the porous diaphragmatic syndrome. It lends support to some of the other theories. Whether these pores are congenital or acquired in the cases of TES is yet to be determined individually as a case of catamenial pneumothorax has been reported in association with Morgagni’s hernia. It is during the menstrual cycle that diaphragmatic endometrial implant congestion takes place followed by intermittent bleeding, the mechanism explaining catamenial hemotorax, followed by necrosis then sloughing of these implants or scarring and fibrosis. In 1991, Shiraishi et al explained the cause of these diaphragmatic fenestrations as the result of these implants sloughing. They usually start as discrete fenestrations that coalesce to form pores that progressively increase in size to the extent that the liver, gallbladder, and colonic herniation through them as shown in several reports.

None of these theories exclusively explain all the varieties of TES or even CP. Bilateral occurrence, right-sided dominance, intact genitals in presence of CP, recurrence after tubal ligation, and other variables have contributed to this dilemma. The author supports the notion of others that it is multifactorial with a combination of these theories. The mechanisms of CP are spontaneous bullae rupture, air passage trans-diaphragmatically, sloughed visceral pleura and air leak, alveolar rupture due to prostaglandin F2alpha broncho-vascular constriction effect, and check valve hyperinflation with rupture as a result.

Pathology. Grossly, these lesions look red, purple, violet, blueberry, brown, white, gray, or even black in color. Usually they are found on the diaphragmatic central tendon. White nodules indicate healing by fibrosis. The endometrial implants represent normal endometrial tissues in the thorax. They consist of stroma and glands in different stages and present in a wide variety of different shapes and sizes. They are lined by pseudo stratified cuboidal epithelium. The glands are of the proliferative type demonstrate inconspicuous nucleoli, scant eosinophilic cytoplasm, and frequent mitosis. The stroma cells demonstrate limited cytoplasm and inflammatory cell infiltration can be seen in association with these features. The endometrial stroma can be found in the lung parenchyma, within the broncho-vascular bundles or outside the alveolar septa. On immunohistochemistry (IHC) examination, the glands stain positively to many cyto keratins including cytokeratin-7, BER-EP4, and nuclear staining for progesterone and estrogen. The stroma stains positively for vimetin frequently and sometimes for desmin, actin, as well as progesterone and estrogen. None have shown any reaction to epithelial or neuroendocrine stains. Pulmonary hemorrhage and hemosiderin containing macrophages indicates a nearby endometriosis.

Epidemiology. The previously reported incidence of catamenial pneumothorax is 3-6% but recent reports from studies including larger patient populations estimate that it occurs in 25-30% of primary spontaneous pneumothoraces in females. Video assisted thoracoscopic surgery (VATS) has contributed greatly to the increased recognition and diagnosis. This estimation does not include the secondary spontaneous pneumothoraces due to chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis, interstitial lung disease, connective tissue disease, bullous lung disease, and noncatamenial primary spontaneous pneumothorax. It can be a right-sided disease (92%), left sided (4.5%) or bilateral (3.5%). Pneumothoraces usually affects an older age group when compared to pelvic endometriosis. The mean age of those affected are in their 3rd or 4th decade of life with age range of 19-45. The average number of attacks before recognition and definitive treatment is 3-5. No genetic or familial patterns have been attributed to this entity.

Clinical presentation. Catamenial pneumothorax has variable presentations. Patients may present with symptoms of endometriosis. Studies have shown that 11% of patients with CP had pelvic surgery or manipulation. Pelvic endometriosis was found in 84% of TES cases when sought after. Moreover, only 30% of CP cases are associated with pelvic endometriosis upon diagnosis. Chest pain (90%), dyspnea (30%), and cough are common respiratory symptoms of CP.
Diaphragmatic pain with radiation to the neck has been reported which could be explained by diaphragmatic endometriosis involvement. The respiratory symptoms are usually mild to moderate in severity but life-threatening cases have been reported. It is usually differentiated from noncatamenial pneumothorax by its milder chest pain, right sidedness, cyclical cough, and timing around menstruation. Ninety percent of patients present within 72 hours of menstruation. Strict temporal synchronicity was observed in 40% of patients and it does not necessarily coincide with every menstruation.

**Diagnosis.** The diagnosis of CP is challenging especially when considering the lack of awareness over the years with the variability of presentations. Therefore, the diagnosis is usually delayed. Moreover, the temporal relation with menstruation is not present in all cases contributing to such delay. There are no specific signs or specific criteria to diagnose CP. Over the recent years and with the utilization of VATS, the awareness has increased and this has led to increased recognition and diagnosis. The definitive diagnosis is achieved by histopathology confirming the presence of endometrial tissues in the thoracic cavity as well as visualization of diaphragmatic fenestrations seen intra-operatively.

**Radiological evaluation.** Plain radiography is not specific and it might demonstrate opacities, nodularity, cavities, cysts, or bullae. Rarely, pneumoperitoneum can be detected. Computed tomography (CT) may demonstrate more detailed findings than plain radiography. They are considered non-specific but if put into clinical context with a high index of suspicion, CT would help in the diagnosis. The CT findings include right-sided pneumothorax, diaphragmatic perforations or nodules, and liver herniation in some cases. The maximal sensitivity is achieved if these radiological images are taken during the menstrual cycle. Chilaiditi syndrome and sign is included in the differential diagnosis of CP where intra-luminal colonic air is misinterpreted as right sided pneumothorax. Magnetic resonance imaging (MRI) has better delineation of thoracic soft tissue components, mainly endometrial implants in the context of CP, but its use is limited in TES. Other modalities might come to use in the future including thoracic ultrasonography especially with its extended use and advanced technology including 3D ultrasonography.

**The role of carcinoma antigen 125 (CA-125) in CP.** Routine laboratory testing of CA-125 is nonspecific and levels may be normal. The role of CA-125 in CP was recognized in recent literature. The production of CA-125 is carried out by endometrial cells and is considered a tumor marker used in colonic and ovarian cancers. The level is notably raised in other benign conditions such as endometriosis, benign ovarian tumors, myoma uteri, and others. The level of elevation was not compared to malignant cases. This could be addressed in future research work. In such conditions, CA-125 would add support to the diagnosis of TES and CP but normal levels do not exclude the diagnosis.

**Management of CP.** Operative or non-operative management are the current options. Currently, surgical management of the condition is not standardized. A shortage of physician awareness in the surgical community with personal bias deferring surgery contributes to this lack of standardization, even in the way surgeons treat primary spontaneous pneumothoraces. The concept of a sequential approach is well-practiced and includes a trial of non-operative management and, if not successful, surgical management. The reverse is also practiced in some institutions. Although these management approaches were never compared head to head, it seems that the outcome is far superior in response to a single arm of management because taking a two-pronged approach to CP management addresses the complex pathogenesis at different levels.

**Non-operative management.** Non-operative management takes into consideration the frequency of CP attacks, their severity, and a patient’s age and fertility desire. The aim is to achieve a state of amenorrhea, pseudo-pregnancy and pseudo-menopause. This will lead to suppression of endometrial tissues whether pelvic or extra-pelvic. Consequently, there is reduction of the burden of the attacks and resolution of symptoms. The concerns with this approach regarding these agents are the lesion location, cost, side effects, fertility, and standard duration. Side effects these medical agents can be troublesome leading to discontinuation. These include virilization, weight gain, osteoporosis, and climacteric symptoms but depend on the agent used. First line treatment includes agents such as danazol, gonadotropin releasing hormone (Gn RH) agonists, and oral contraceptives. Danazol is a derivative of the synthetic steroid ethisterone, a modified progestogen, which causes anovulation by attenuation of mid-cyclic luteinizing hormone (LH) secretion. This leads to increased levels of testosterone explaining the androgenic side effects. Liver damage has been reported as a potential side effect.

The GnRH agonists, on the other hand, create a state of deficient follicular stimulating hormone (FSH) and LH secretion. This state leads to hypogonadotropic
hypogonadism. The main side effects are mainly related to hypoestrogenism, which can by ameliorated by estrogen or progesterone replacement.14

Oral contraceptives create a state of imbalanced hormonal environment unable to support sound function for endometrial tissues. They are the least expensive yet least effective compared to the former two agents.56 The relation of CP attacks with the use of clomiphene citrate and other ovarian stimulants is documented in the literature towards aggravation of symptoms and attack frequency.6

There is no standard regimen to this approach in terms of the agents used, duration of such treatment, and timing and indications of crossover to operative management. A major limiting factor in all these proposed protocols is the side effects and fertility desire. Recent literature recommends a 6-12 months of treatment as shorter trials failed to show efficacy and a longer duration would potentially cause side effects and intolerance in some patients.5,56 Recurrence is high in the conservative approaches and recurrence of up to 50% have been reported if the medical agent is used alone without surgery, regardless of the agent used.1,2,14,59 Nevertheless, if a medical agent is used after surgery for 6-12 months this rate drops to around 5%.41 Therefore, it is clearly indicated that the combined approach of management is superior.57

Operative management. In general, the classical indications for surgery were considered when failure of non-operative treatment takes place with persistent symptoms or recurrence and intolerance or side effects to medications.2,3 Some authors attributed this failure to incomplete suppression of endometrial tissues due to short duration or lack of effective dosing to avoid side effects.24 Many new concepts have been introduced in the surgical management of CP. Axillary thoracotomy and standard thoracotomy were mainstays of the surgical treatment.43 Varying results were produced because they addressed part of the pathology. For instance, axillary thoracotomy missed diaphragmatic inspection and intervention and addressed only apical bullae, which is not the case in many patients.42,43 In 1990, VATS was introduced with limited use by many surgeons initially. Diaphragmatic fenestrations, bullae excision, pleurodesis, tubal ligation, or hysterectomy are all considered part of the surgical armamentarium to treat CP with variable improvement in the outcome.24,44 Diaphragmatic fenestrations are believed to play a major role and not addressing them will not achieve cure or reduction in recurrence rate, especially that they are found in 20-49% of CP patients.37,58 In Japanese literature it approached 66% of CP cases.37 This demonstrates regional variation and a multinational registry would help in that regard to reduce such variability in practice. Moreover, diaphragmatic intervention improves the outcome. Other intraoperative findings include diaphragmatic lesions (38%), visceral pleural lesions (29.6%), and a combination of lesions (8.6%). No lesions were diagnosed in 8.6% of cases and this could be the result of sloughing of lesions and inability to visualize them.44 Diaphragmatic lesions included endometrial implants and fenestrations in combination or alone. The most common is fenestration without endometrial implants (42%), followed by combination of both (31%), and then endometrial implants without fenestration (26%).44 For these diaphragmatic implants, the surgical interventions include direct suturing of these fenestration, endoclipping of small fenestration, application of glue to seal the fenestration (they only address the current ones but not the ongoing pathology), excision of the diaphragmatic involved part with primary repair, diaphragmatic placation, or mesh coverage or excision with mesh repair.14,43,44 In the visceral pleura, implants are rarely seen but bullae, blebs, or scars can be seen as a single or multiple foci in up to 30% of cases or not seen at all in some.1,2,42,44,56 Surgical options for the visceral pleura include wedge resection, anatomical resections ranging from segmentectomy to lobectomy.24,44 Hydro-dissection, laser, or vaporization are reported options to address superficial lesions but none of these achieved superior status to be a standard option.2 An alternative approach includes pleurodesis that can be achieved chemically by talc, povidone-iodine, or mechanically by abrasion or cautery.39,44,56,57 Pleurectomy is considered by some authors especially in multiple recurrent cases.37,44 Pleurodesis especially with talc is reported to be an effective adjunct to management.39 Better magnification is provided by VATS for inspection of the thoracic cavity, allowing the performance of all the previously mentioned surgical options except the diaphragmatic mesh repair, which could be difficult to achieve. At such point, a thoracotomy is undertaken.42 None of these surgical options have proven to be effective alone especially pleurodesis which is still practiced by some surgeons.43 The surgical mortality is very rare and no significant morbidity has been reported. Surgery confirmed the diagnosis of CP in 60% of cases while the rest are overlooked or undiagnosed.24 Some authors consider laparoscopy to investigate and manage pelvic and peritoneal endometriosis as well as to consider tubal ligation if fertility is not desired.59 Hysterectomy as definitive treatment is a radical management option considered in multi-location endometriosis by some authors.2,3
**Outcome and prognosis.** There is a general consensus towards the combined approach with sequential operative and non-operative management options. The goal of this management is to resolve the symptoms, reduce the severity of symptoms, reduce recurrence rates, fulfill fertility desire, and ultimately to achieve a cure. So far, there are no uniform outcomes and no comparative studies to address the effects of different surgical options available. The lack of a standardized approach or reporting hinders conclusions to a superior treatment protocol. A solid fact remains, that the recurrence is high approaching 40-50% if medical treatment is given as a sole line of management with a mean follow-up period of 52 months (range 14-168 months). This is reduced significantly when combined with surgical options such as pleurodesis and diaphragmatic excision with mesh repair to as low as 5-8% with a follow-up of up to 45 months.1

**Controversies and concerns.** Does pelvic endometriosis always present with CP? Reports and studies show that if looked for, the detection rate increases but currently, the literature states that spontaneous pneumothoraces in females is around 22-37%. The reported recurrence rate of 21% after diaphragmatic intervention demonstrates the need for a medical modality to control endometriosis.21 Whether or not to standardize medical therapy after surgery remains to be determined. The issue of prophylactic hormonal therapy was raised especially in high-risk patients with endometriosis and patients with parenchymal involvement.57 When 60% of confirmation comes as a result of surgical exploration and intervention, this leads to the slight preference of a surgical-medical sequential approach.3 Tubal ligation and hysterectomy showed variable results from lack of efficacy to cure.60 Endometrial tissues might not be found and this does not preclude the diagnosis of CP.61 The observation of thoracic endometriosis occurring during pregnancy without prior history of endometriosis raises the possibility of yet another mechanism of the disease or a combination of factors. Some associations such as with Bernard-Horner’s syndrome could explain these and multifocal intra-thoracic endometriosis.62,63

In conclusion, catamenial pneumothorax is not rare but rather overlooked and under-diagnosed. Better understanding came from increased reporting of cases and outcomes. Theories were described raising the possibility of combined pathogenesis rather than a single explanation although the migration and micro-metastasis theory seems most plausible. Cases can be better captured by a high index of suspicion and obtaining detailed gynecological history in any

![Figure 1 - Suggested algorithm for catamenial pneumothorax (CP) management approach. VATS - video assisted thoracoscopic surgery. Rt - right, CA-125 - carcinoma antigen 125, CXR - chest x-ray, VATS - video-assisted thoracoscopic surgery](Image)
ovulating female even in the absence of endometriosis. Supportive laboratory investigation including CA-125 can improve the detection of these patients. The combined medical and surgical option has shown better results in terms of cure and reduced recurrence rates. Combining detection and therapeutic approaches in a standardized multicenter, multi-national registry would improve our understanding of the disease and refine our therapeutic protocols.

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