review article

Wien Klin Wochenschr (2017) 129:717–726
DOI 10.1007/s00508-017-1237-4

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Catamenial pneumothorax since introduction of video-assisted thoracoscopic surgery

A systematic review

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Received: 10 December 2016 / Accepted: 8 July 2017 / Published online: 31 July 2017

Summary
Background Catamenial pneumothorax is an uncommon form of spontaneous pneumothorax in women. The exact epidemiology and pathogenesis remain elusive. Video-assisted thoracoscopic surgery is used for diagnostic and therapeutic purposes.
Objective The aim of this review was to analyze the demographic features, intraoperative findings, treatment methods and outcome in catamenial pneumothorax patients. In addition, we assessed the relationship between catamenial pneumothorax and pelvic endometriosis.
Search strategy A PubMed search of medical literature, published from January 1993 (video-assisted thoracoscopic surgery first described in literature) to January 2015, using the keywords "catamenial pneumothorax" was performed. Our study complied with the preferred reporting of items for systematic reviews and meta-analysis principles. A total of 182 patients were included in the analysis, including 4 patients treated at our institution.
Selection criteria The inclusion criteria of were recurrent (at least two) episodes of spontaneous pneumothorax in relation to onset of menses.
Data selection and analysis Age at time of diagnosis, side affected, diagnosis of pulmonary endometriosis, intraoperative findings, histological confirmation of thoracic endometriosis, methods of treatment and outcome were recorded.
Main results In 2.9% of the patients no pathological lesions were found; however, 59.3% had endometrial implants and 57.0% diaphragmatic perforations. Pelvic endometriosis was reported in 39.5% patients. Patients with diagnosed pelvic endometriosis showed a significantly higher rate of endometrial implants and histologically confirmed endometriosis lesions than patients without pelvic endometriosis. In 26.9% of patients, recurrence was observed after treatment.
Conclusion Video-assisted thoracoscopic surgery provides good diagnostic and therapeutic results; however, 25% of patients experienced recurrence despite adequate treatment. A strong association exists between thoracic and pelvic endometriosis in catamenial pneumothorax patients.

Keywords Catamenial pneumothorax · Thoracic endometriosis · Pelvic endometriosis · Video-assisted thoracoscopy

Contribution to authorship All authors participated in the making of this study; all contributed to the conception and design of the study, acquired, analyzed and interpreted data. All participated in the drafting and approved the final version of the study. Furthermore, all agree to be accountable for all aspects of the work.

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Introduction

Catamenial pneumothorax (CTPX) is a form of recurrent spontaneous pneumothorax that repeatedly occurs in women of reproductive age [1–3]. Pneumoth-

orax in association with menses was first described by Maurer et al. in 1958 [4], the term CTPX was coined by Lillington et al. in 1972 [5], catamenial deriving from Greek meaning "monthly". It is most commonly associated with endometriosis, but other etiological mechanisms of the disease exist [1, 2, 6]. CTPX is the most common form of thoracic endometriosis syndrome, which also includes three other clinical presentations: catamenial hematothorax, catamenial hemoptysis and endometrial lung nodules [1, 3]. In the literature, CPTX is typically defined as recurrent pneumothorax occurring up to 24 h before or within 72 h after onset of menses [2, 3, 7]; however, not necessarily every month [8]. A high level of clinical suspicion has to be maintained since symptoms and signs of CTPX are unspecific [9]. So far CTPX has been considered a rare entity; however, recent findings indicate that it is the cause for about one third of all surgically treated cases of pneumothorax in women [3, 10–12]. Due to the small number of studies, discussions about the best treatment of patients with CTPX are inconclusive. In the light of this matter, it is of great importance to obtain up to date information. Relating to this issue, the rationale of our study was to update the current knowledge on CTPX, since the last systematic review was performed in 2004 [8].

The first reports of video-assisted thoracoscopic surgery (VATS) used in diagnosis and treatment were published in 1992 [13–19]. Before that, surgical management of recurrent spontaneous pneumothorax was axillary thoracotomy with apical pleurectomy, which did not always allow appropriate inspection of the diaphragm [9, 20]. VATS provides magnification and exposure of possible defects, which may facilitate recognition and identification of lesions [7, 8, 21], whilst allowing exploration of the whole thorax [3] together with tissue sampling for histologic confirmation of thoracic endometriosis (TE) [10]. Several studies suggested that VATS is preferable to open thoracotomy due to shorter postoperative hospital stay [22, 23] and less postoperative pain, leading to shorter recovery time [23, 24].

The aim of our study was to assess demographic features, intraoperative findings, treatment methods and outcome in CTPX patients by systematically reviewing the literature since VATS introduction. Furthermore, we attempted to assess the relationship between CTPX and pelvic endometriosis (PE). The results of our study could be useful in management and treatment of CTPX patients.

Methods

The National Medical Ethics Committee approved the study. We conducted a PubMed search of medical literature, published from January 1993 to January 2015, using the key term "*catamenial pneumothorax*". Our study complies with the preferred reporting items for systematic reviews and meta-analysis principles [25].

Study criteria

The studies included in our analysis had to meet the following criteria: recurrent (at least two) episodes of spontaneous pneumothorax, when reported symptoms occurred in relation to the onset of menses [7, 26]. Studies were excluded based on the following criteria: reviews and editorials, non-English studies providing uninformative English abstract, comments on previous studies, author replies and letters to the editor. If a specific patient description did not meet the study inclusion criteria in the case series studies, then the patient was excluded.

Data extraction

For eligible studies, the following data were extracted: surname of the first author, year of publication, age of the patient, affected side, intraoperative findings, histological confirmation of TE, diagnosis of PE, treatment method, type of surgical intervention, type of hormonal treatment, gynecological procedure, follow-up time, recurrence of pneumothorax and number of recurrences.

Statistical analysis

The χ^2-test was used to compare groups according to the presence of PE and diaphragmatic perforations. A Student's two -tailed *t*-test was utilized to compare patient age according to intraoperative findings and according to the presence of concomitant PE. Comparison of main intraoperative findings and treatment type in patients with recurrence was made with analysis of variance (ANOVA). Post hoc comparisons were made with Bonferroni correction. Significance was set at $P < 0.05$. Statistical analysis was performed with SPSS v.17.0 (SPSS, Chicago, Ill).

Results

Literature search

The process of identifying eligible studies is summarized in Fig. 1. A total of 182 papers were identified in the initial search. After examining titles and abstracts 12 review papers were excluded along with 42 non-English studies providing non-informative English abstracts and 27 studies for not meeting selection criteria. A total of 101 papers were included in this systematic review [2, 6–9, 12, 21, 27–120], 15 of these were non-English language studies providing informative English abstracts [27–41]. Included papers were mostly individual case reports, however, there were 18 case series (the size ranged from 2 to 12 patient descriptions). After carefully reading the case series full texts, an additional 10 patients were excluded for not meeting the inclusion criteria. After including 4 pa-

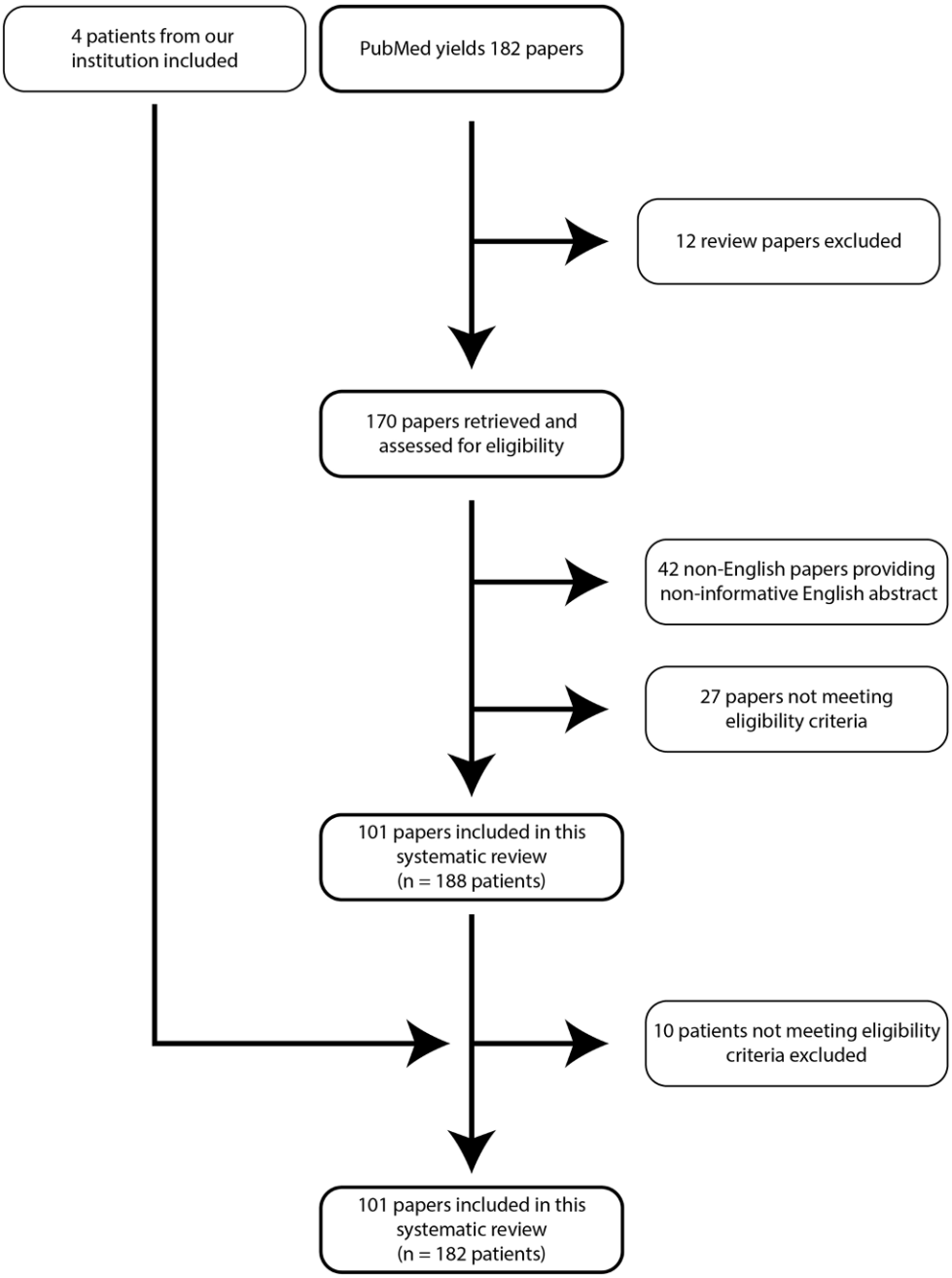

Fig. 1 Flowchart of the systematic search and the review process

tients treated at our institution a total of 182 patients were included in this systematic review.

Demography and affected side

At the onset of symptoms, the mean age of patients presenting with CTPX was 36.5 ± 6.8 years (range: 19–51). The mean age at CTPX presentation in patients with concurrent diagnosis of PE was 36.6 ± 6.1 years (range: 19–46). No difference in the age of CTPX presentation was observed between the patients with and without concurrent PE ($P > 0.05$). Information regarding the affected side of the lungs was reported in 181 (99.5%) patients. The majority of cases of pneumothorax presented as unilateral (95.6%): right sided in 170 (93.9%) patients and left sided in 3 (1.7%) patients.

Intraoperative findings

Adequate information on intraoperative findings was reported in 172 (94.5%) patients (Table 1). Fig. 2 shows age frequency distribution of the reviewed patients and main intraoperative findings (endometrial implants, diaphragmatic perforations and blebs/bullae). No significant effects were found between intraoperative findings and patient age (all $P > 0.05$).

Table 1 Percentages of main intraoperative findings in patients with catamenial pneumothorax published in the literature

Endometrial implants	59.3
Diaphragmatic perforations	57.0
Blebs/bullae	30.2
Diaphragmatic perforation plus endometrial implants	34.3
Endometrial implants plus blebs/bullae	14.0
Diaphragmatic perforation plus blebs/bullae	11.6
Diaphragmatic perforation plus blebs/bullae plus endometrial implants	8.7
No pathological findings	2.9
Histology confirmed TE	52.3

TE thoracic endometriosis

In the diagnostic work-up, coincidental pulmonary neoplasms were found in 3 (1.7%) patients: all had non-small cell lung cancer and 2 were lepidic adenocarcinomas. In patients with adequate intraoperative information, PE was reported in 68 (39.5%) patients. When dividing these patients with respect to the time at CTPX presentation, the following distribution was observed: in 46 (67.6%) patients PE was diagnosed before, in 5 (7.4%) patients PE was diagnosed after and in 17 (25.0%) patients PE was diagnosed at the time of CTPX presentation. Table 2 shows a comparison of the intraoperative findings in patients with and without diagnosis of PE.

Treatment methods

Adequate information on surgical interventions was reported in 168 (92.3%) patients (Table 3). A specific type of pleurodesis was not given for in 5 patients. Pleurodesis was subdivided by type: 84.1% underwent surgical, 32.6% chemical and 16.7% combined pleurodesis. Adequate information on the type of hormone treatment was reported in 124 (68.1%) patients (Table 3): 114 (62.6%) patients opted for the combination of VATS and hormone treatment.

Of the patients five refused the recommended medical therapy: two declined both surgical and hormonal treatment, whilst three agreed to VATS, but refused hormone therapy thereafter. Hysterectomy with bilateral salpingo-oophorectomy was performed in 12 (6.6%) patients: 9 of the patients had concurrent PE diagnosis, whilst 3 did not.

Outcome

Detailed follow-up time indicating treatment outcome was available for 134 (73.6%) patients. Mean follow-up time was 23.8 ± 21.2 months (range: 1–120 months). In 36 (26.9%) patients, recurrence was observed after the final treatment. The mean value of recurrences was 1.65 ± 1.23 (range: 1–6). Subanalysis of this group of patients showed that 18 (50.0%) patients also had PE diagnosis, 29 (80.6%) patients had combined treatment with VATS and hormone therapy, 3 (8.3%) patients opted for hormonal treatment alone and 4 (11.1%) patients underwent VATS only. The mean follow-up time of patients with recurrence of pneumothorax was 28.6 ± 25.3 months (range: 3–120) and 98 (73.1%) patients did not suffer from disease recurrence after the final treatment with the follow-up time of 22.4 ± 19.6 months (range: 1–110). No significant differences between the main intraoperative findings (endometrial implants, diaphragmatic perforations and blebs/bullae) and recurrence were observed ($P > 0.05$). When dividing patients according to the presence of diaphragmatic perforations, no signif-

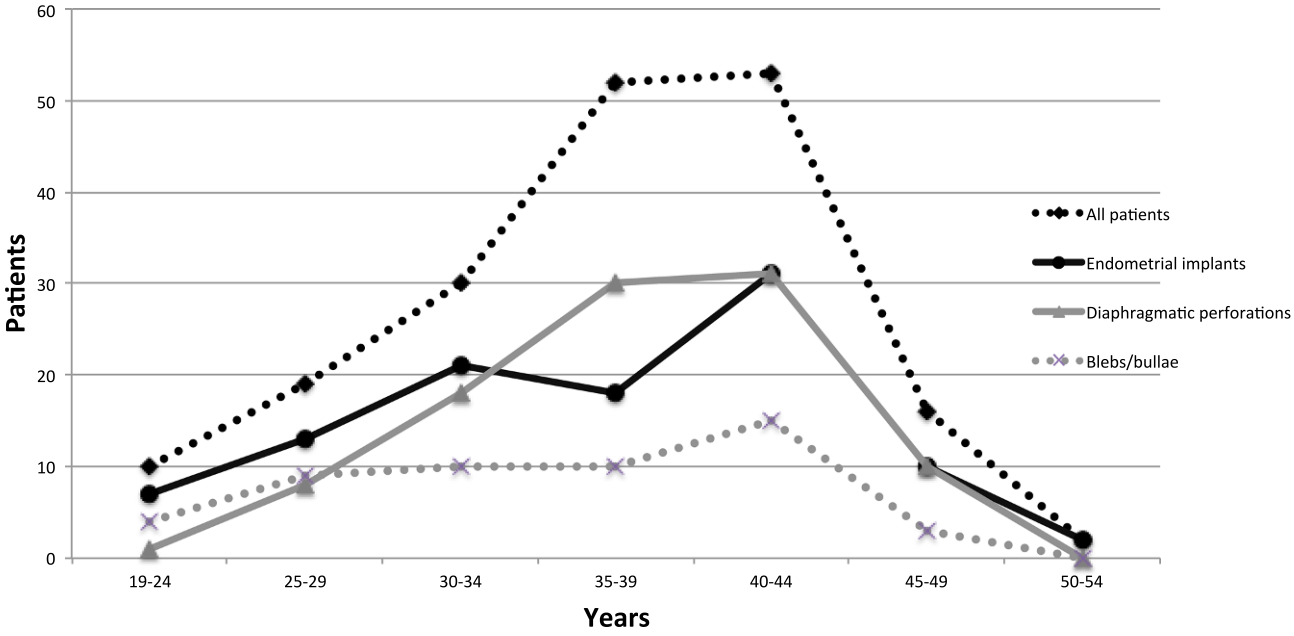

Fig. 2 Graph demonstrating age frequency distribution of the main intraoperative findings and reviewed patients

Table 2 Comparison of the intraoperative findings in patients with and without diagnosis of pelvic endometriosis

	Diagnosis of PE (%) ($n = 68$)	No diagnosis of PE (%) ($n = 104$)	*P* value
Endometrial implants	73.5	51.0	0.003*
Diaphragmatic perforations	55.4	56.6	NS
Diaphragmatic perforations plus endometrial implants	36.2	26.8	NS
Blebs/bullae	25.0	33.6	NS
Endometrial implants plus blebs/bullae	14.7	13.5	NS
Diaphragmatic perforations plus blebs/bullae	13.2	10.5	NS
Diaphragmatic perforations plus blebs/bullae plus endometrial implants	11.8	7.7	NS
No lesions	1.4	3.8	NS
Histologically confirmed TE	58.8	43.3	0.046*

PE pelvic endometriosis, *NS* not significant, *TE* thoracic endometriosis
*Statistically significant

Table 3 Type of surgical interventions and hormonal treatment used in catamenial pneumothorax treatment reported in the literature

Surgical interventions	(%)	Hormonal treatment	(%)
Pleurodesis	81.0	GnRH agonist	56.5
Diaphragmatic interventions	65.5	Hormone contraceptives	25.8
Diaphragm resection	18.5	GnRH agonist plus progesterone	25.8
Diaphragm suture	26.8	Progesterone	18.5
Diaphragmatic plication, mesh, etc	20.2	Danazol	4.0
Lung resection	23.2	Other	7.2
Apical wedge lung resection	17.3		
Middle lobe resection	2.4		
Wedge resection (not defined)	3.0		

GnRH gonadotropin-releasing hormone

icant difference in outcome was observed ($P > 0.05$). Furthermore, no significant differences between treatment type as well as hormonal treatment type and recurrence were observed ($P > 0.05$).

Discussion

We performed a systematic review of the literature on CTPX in order to review demographic features, intraoperative findings, treatment methods and outcome. In addition, we attempted to assess the relationship between CTPX and PE.

A number of theories have been proposed to explain the pathogenesis of this peculiar disease. The first theory proposes that the cause of pneumothorax is endometriosis and cyclic tissue breakdown, which affects about 10% of women in reproductive age [121]. The clinical picture depends on the anatomic location of the implants, which bleed during menses and die off. Implants may cause perforations in visceral pleura resulting in pneumothorax [115]. The second theory proposes that cyclic necrosis of hormonally induced diaphragmatic endometrial tissue can produce acquired diaphragmatic fenestrations [1, 122]. Fenestrations cause transdiaphragmatic passage of air and resultant pneumothorax in relation to absence of cervical mucus plugs during menses, uterus contractions, physical activity or sexual intercourse [1]. The third theory describes an increased likelihood of ruptures of bullae and alveolar ruptures due to hormonal changes during menses [98, 115]. In the fourth and last theory, increased prostaglandin F2α during menses may cause vasoconstriction and bronchospasm with subsequent alveolar rupture and pneumothorax [123]. None of these theories can fully explain all of the clinical pathological forms of CTPX; therefore, the cause of the disease is likely to be multifactorial [10].

Demography and affected side

We showed that the mean age of patients presenting with CTPX is 36.5 years, which is in accordance with previous published review studies [1, 8, 124]. The predominance of right-sided pneumothorax in over 90% of patients was observed in all larger review studies [1, 3, 8, 21, 55, 124], which is in accordance with our result of 93.7%. Right sided predilection may be explained by specific movements of fluid in the peritoneal cavity, where peritoneal fluid "circulation" promotes the flow of fluids (e.g. pus, cell aggregates and air) from the pelvis to the right sub-diaphragmatic area, which may suggest diffusion of endometriosis from the pelvis through the right diaphragm into the right thoracic cavity [125].

Pathological findings

No pathological findings were found in only 2.9% of patients. Most frequent pathological findings were endometrial implants (present in 59.3% of patients) followed by diaphragmatic perforations (in 57.0% of patients). The reported occurrence in previous analyses of endometrial implants and diaphragmatic perforations were: 13% and 26% [1], 52.1% and 28.6% [8], 57% and 53% [124], respectively. An increasing trend of identified pathological findings in CTPX patients can be recognized over the years, with the highest rate presented in our study. This may be attributed to the enhanced interest in VATS, which has become an indispensable method in the diagnosis and treatment of CTPX [2, 8, 26]; however, this increasing trend cannot be assigned solely to VATS. Disease awareness with correct VATS timing in the menstrual cycle and surgeon experience are important factors that need to be considered [21, 26, 52].

Interestingly, only a slight predominance of endometrial implants over diaphragmatic perforations was observed; however, a different pattern was observed in age frequency distribution between endometrial implants and diaphragmatic perforations. The most pronounced difference can be observed in age group of 35–39 years with the predominance of diaphragm perforations; however, this difference levels off in the age groups over 40 years. Interestingly, the pattern of blebs/bullae follows the pattern of endometrial implants; however, both are concomitantly present in only 14.0% of patients. The observed pattern association may be explained by a recent study by Kawaguchi et al. who described findings of endometrial cells around lung bullae, suggesting a possible new mechanism for CTPX in which cyclic endometrial shedding in the lungs could cause destruction of the alveolar epithelial lining and form bullae [126].

Previous studies have shown that 28.8% of patients with CTPX have concurrent PE, whilst 61–85.7% of patients who undergo laparoscopy or laparotomy are diagnosed with PE [1, 127]. Our review shows that 39.5% of patients had a diagnosis of concurrent PE. Two thirds of these patients had PE diagnosed prior to CTPX presentation, others were diagnosed at CTPX presentation or during the follow-up. No difference in the age at CTPX presentation was observed between patients with and without PE. Soriano et al. emphasized in their study that an evaluation of the pelvis in patients, presenting with thoracic endometriosis syndrome or CTPX is necessary to rule out possible concurrent PE [127].

The strong association between PE and TE has led many to believe that the primary source of ectopic endometrial tissue in the thorax may originate from PE [1, 12, 125, 127–129]. In order to expand this idea, we have divided patients according to the diagnosis of PE and compared the intraoperative findings between the groups. Patients with PE diagnosis showed a significantly higher rate of endometrial implants and histologically confirmed TE compared to patients without PE diagnosis. Interestingly, no significant differences were observed for other pathological findings. This shows a strong association between TE and PE in CTPX patients; however, the high percentage of endometrial implants and histologically confirmed TE in the group of patients without diagnosis of PE suggests alternative mechanisms need to be considered as well. In the diagnostic work-up, coincidental pulmonary neoplasms were found in 1.7% of patients. This is within the limits of expected 6.2% lifetime probability of developing lung cancer in females [130]; however, it suggests an attentive diagnostic work-up has to be performed in these patients.

Treatment methods

Over 90% of patients were treated surgically and approximately two thirds of patients underwent a combination of hormonal and surgical treatment. Pleurodesis was the most common intervention, which is in accordance with a previous review study [8]. The majority of pleurodesis performed were mechanical (abrasion or pleurectomy), which have been proven to be more successful in comparison to chemical pleurodesis [131].

In contrast to the review from 2004, our review shows an important increase in diaphragmatic interventions in surgically treated patients from 38.8% to 65.5% [8]. None of the specified subtypes of diaphragmatic interventions were proven to be superior in comparison to others in terms of outcome. The presence of diaphragm perforations has been reported to be a significant factor for recurrent pneumothorax and coincides with the second theory for CTPX etiology, where transfallopian passage of air through diaphragmatic perforations causes pneumothorax [2, 7, 8]. It has been suggested that repair of such defects could prevent transfallopian ascent of air, which may be a possible reason for the observed increase of diaphragmatic interventions in recent years [8, 132]; however, several previous case reports did not link the repair of diaphragmatic defects with disease prevention [3, 9, 133]. Furthermore, no association has been made between diaphragm fenestrations and recurrent pneumothorax in previous reviews [1, 124]. Similar observations were made in our study, since no significant effect of main intraoperative findings on pneumothorax recurrence was observed.

In 6.6% of patients hysterectomy with bilateral salpingo-oophorectomy was performed. Despite being an effective treatment of endometriosis, the low percentage is understandable, since it should be considered only when other treatment methods fail and in women who no longer wish to conceive. Symptoms may however recur due to dormant thoracic endome-

trial implants that can be reactivated with exogenous estrogen [1, 84, 134, 135].

Outcome

Recurrence is the most common complication of CTPX, with reported recurrence rates of 20–40% [3, 12, 21, 52]. Our study shows that approximately one quarter of patients have disease recurrence in 2 years and half of these patients have concurrent PE diagnosis. There is a consensus that drug treatment with GnRH analogs in the immediate postoperative period for 6–12 months [3, 7, 9, 10, 52, 55, 136] is a helpful adjunct to surgery to prevent recurrences. We showed that over half of the patients opted for GnRH agonists. In a single centre study, Marshall et al. observed that in contrast to hormonal therapies that allow for menses, GnRH agonist therapy effectively suppresses CTPX recurrence [12]; however, in our study no significant effect of hormonal type treatment on pneumothorax recurrence was observed.

Limitations

A few limitations of our review should be noted. We could not discern in the reports whether the timing of diagnostic procedures in all of the published case studies was optimal. Endometrial implants bleed and die off due to cyclical hormonal changes [2, 7]; therefore, VATS should be ideally carried out at the beginning of menstrual flow, when the endometrial implants are most expressed [1, 7]. Incorrect timing would therefore have the potential for underdiagnosis. Since our analysis was based on numerous case reports, published by different authors within a large time frame, the lack of uniformity in patient examination and surgical procedures may have affected the final results.

Conclusion

Endometrial implants and diaphragmatic perforations occur at a similar rate, however have different age frequency distribution patterns. VATS provides good diagnostic and therapeutic results, although approximately one quarter of patients have disease recurrence within 2 years after treatment. A strong association exists between TE and PE in CTPX patients, however alternative mechanisms need to be considered.

Compliance with ethical guidelines

Conflict of interest K. Bricelj, M. Srpčič, A. Ražem and Ž. Snoj declare that they have no competing interests.

Ethical standards The Slovenian National Medical Ethics Committee approved our study on 15 September 2015 (reference number: 0120-509/2015-2, KME 79/09/15). Our study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All procedures followed were in accordance with ethical standards of the responsible committee for human experimentation.

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