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True Prevalence of Diaphragmatic Endometriosis and its Association with Severe Endometriosis: a Call for Awareness and Investigation

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Abstract

Study Objective: To identify characteristics indicating preoperatively the presence of diaphragmatic endometriosis (DE).

Design: Comparison of characteristics of patients with DE with characteristics of patients with abdominal endometriosis without diaphragmatic involvement, in a prospective cohort study.

Setting: Tertiary referral center; endometriosis center.

Patients: 1372 patients with histologically proven endometriosis.

Interventions: Surgery performed laparoscopically under general anesthesia. All patients with suspected endometriosis underwent a complete bilateral inspection of the diaphragm.

Measurements: Demographic and clinical pathologic characteristics were evaluated using basic descriptive statistics (comparison of the groups using the chi-square test and the Mann-Whitney t-test). A logistic regression analysis was performed to evaluate the relationship (hazard ratio) between symptoms and the presence of DE.

Main Results: DE was diagnosed in 4.7% of the patients (65/1372). There was no significant difference between the two groups (patients with abdominal endometriosis with or without DE) with regard to typical endometriosis pain (dysmenorrhea, dyschezia, dysuria, and/or dyspareunia). However, in the DE group, diaphragmatic pain was present significantly more often pre-operatively (27.7% vs 1.8% p<.001). Four DE patients (6.1 %) were asymptomatic (with infertility the indication for surgery).

In the DE group, 78.4 % had advanced stages of endometriosis (rAFS III° or IV°); the left lower pelvis was affected in more patients (73.8%). In cases of ovarian endometriosis, patients with DE showed a significantly higher prevalence of left ovaries involvement (left 63% vs right 35.7%, p<.001). Patients with DE had a significantly higher rate of infertility (49.2% vs 28.7%, p<.05).

Conclusion: Patients with shoulder pain, infertility, and/or endometriosis in the left pelvis have a significant higher risk of DE and therefore need specific preoperative counseling and if indicated surgical treatment.

Keywords: Abdominal endometriosis; diaphragmatic endometriosis; diaphragmatic pain; endometrial lesions; menstrual reflux theory; ovarian endometriosis; shoulder pain.

Introduction

Endometriosis is a common condition with a wide range of symptoms, characterized primarily by the presence of endometrial-like glands and stroma outside the uterine cavity. It is believed to affect 6%–10% of reproductive-age women (1, 41, 42). Endometriosis lesions located in the abdominal area are found predominantly in the pelvic area and, less frequently, in the upper abdomen. They are found only rarely in extra-abdominal organs such as lungs, skin, or the spinal cord (1, 31, 32, 33, 36, 37, 40).

Diaphragm endometriosis (DE) is a distinct condition first described by Brews in 1954 (2). Its prevalence is judged to be between 0.19% and 1.5% of all intra-abdominal endometriosis lesions (3, 4, 35).

The pathogenesis of DE can be explained by the menstrual reflux theory: transportation of viable endometrial cells in peritoneal fluid follows a characteristic clockwise circulation pattern, from the left pelvis up to the right diaphragm, where endometrial cells implant more easily, because their movement is constrained by the falciform ligament (5, 25, 38, 44). Alternative hypotheses include the following: 1) the coelomic metaplasia hypothesis that endometriosis arises by metaplasia of mesothelial cells lining the pleura and peritoneal surfaces into endometrial glands and stroma (1); 2) the theory of benign metastasis, by which ectopic endometrial implants are the result of lymphatic or hematogenous dissemination of endometrial

cells (1, 28); and 3) the steam cell theory, which presumes that de-novo development of endometrial tissue occurs from endogenous stem cells in the endometrium (28). The genetic/epigenetic theory, the repeated tissue injury and repair caused by uterine hyperperistalsis, and a fetal or adolescent origin have been also suggested (39).

Symptoms of patients with DE are often nonspecific, multifactorial, and not always well defined. Classic DE symptoms such as dyspnea, cough, upper abdominal pain, or shoulder pain due to phrenic nerve irritation occur in only 25% of cases (4, 6).

The diagnosis of DE is challenging (1, 10). DE is often detected incidentally during laparoscopic surgery for pelvic endometriosis (38). It is not known why some patients with DE are symptomatic while others remain asymptomatic (7). Preoperative abdominal ultrasound detects DE in only 15% of cases. MRI is the most accurate imaging modality to detect DE, as well as thoracic endometriosis, with a sensitivity of 80% .(8, 25, 26, 34, 35). Due to the often unspecific symptoms, unclear pathogenesis, and the difficult diagnosis, more knowledge is needed about this rare disease. In addition, since DE is often detected incidentally during laparoscopic surgery for pelvic endometriosis, more clinical knowledge should be gathered (36, 38). Given the complexity of treatment, early diagnosis is important.

The aim of the study was to evaluate the prevalence of DE in a large cohort and identify risk factors such as demography, abdominal localization, endometriosis symptoms, and other symptoms that help identify patients with DE preoperatively.

Material and Methods

The certified endometriosis and tertiary referral center of the Bern University Hospital

has collected prospectively data on all patients with surgically confirmed endometriosis since January 1997. For this study, information on patients diagnosed with DE up to December 2021 was extracted from the data base. The characteristics of patients with DE were compared with those of patients without DE: demographic data, stage of endometriosis, state of fertility (infertility defined as desire for pregnancy since longer than 12 months), endometriosis symptoms, location/distribution of endometriotic lesions, and surgical treatment. In our cohort, endometriosis was classified according to the revised American Fertility Society (rAFS) classification, and deep-infiltrating endometriosis was classified additionally according to the ENZIAN score (applied since 2012).

Surgery was performed laparoscopically with a 30° Optic under general anesthesia. All patients with suspected endometriosis underwent a complete inspection of the diaphragm bilaterally in prone position, documented by photos and videos. Atraumatic grasping forceps were used to push the liver down; a steep reversed Trendelenburg position was used if needed. If a sentinel endometriosis was found or a DE was strongly suspected, the liver was mobilized with incision and section of the round and the falciform ligament toward its apex (12). The liver was then pushed to the left side if necessary, using an Endo Paddle Retract of Covidien-Medtronic. With this technique, complete visualization of the posterior diaphragm is possible. Removal of a diaphragmatic lesion was performed through vaporization with a carbon dioxide laser (15-20 Watt) if it was superficial, or through excision with repair of the defect if the lesion was deeply infiltrated the diaphragm.

Statistical Analysis

Statistical analysis was performed using SPSSS Version 25.0 (IBM®). Demographic and clinic pathologic characteristics were evaluated using the basic descriptive statistics with comparison of the groups using the chi-square test and the

Mann-Whitney t-test. All p values were two sided, and p-values <.05 were considered to be statistically significant. A logistic-regression analysis was performed to evaluate the relationship (hazard ratio) between symptoms and the presence of DE.

Results

Out of a total of 1372 patients who underwent a diagnostic laparoscopy and were diagnosed with endometriosis on the basis of inspection of the whole abdominal cavity, 65 patients were diagnosed with DE, an incidence of 4.7%.

In our cohort, DE was often associated with severe endometriosis (rAFS III° or IV°) (78.4%). rAFS III: OR= 6.312, 95% CI (2.139-18.624), rAFS IV: OR= 4.554, 95% CI (1.582-13.109).

Patient characteristics

In 1305 of the 1372 patients, prospectively documented information on rASF was available. Comparison of patients with and without DE revealed a significant difference in the stage of the endometriosis, according to the rAFS classification (Table 1). In the DE group, 78.4 % had an advanced stage of endometriosis (rAFS III° or IV) (Figure 1). We identified more patients with the left lower pelvis affected: rAFS II: OR= 4.853, 95% CI (1.543-15.265), rAFS III: OR= 6.312, 95% CI (2.139-18.624), rAFS IV: OR= 4.554, 95% CI (1.582-13.109).

Location of the endometriosis

Consistent with the literature, the right diaphragmatic side was more often affected, i.e., in 92.3% of the DE patients (60/65) (25). Regarding ovarian endometriosis, patients with DE showed a significantly higher prevalence of left ovaries involvement (left ovaries 63% vs right ovaries 35.7%, p<.001). Left side OR=11.206, 95% CI (2.369-52.992), right side OR = 6.479, 95% CI (1.469-28.567), both sides rAFS III: OR = 0.802, 95% CI (0.690-0.933) (Table 1).

Symptoms

Patients with DE had a significant higher rate of infertility than patients without DE (49.2% vs 28.7% p<.05?). There was no significant difference between the groups in terms of age and in terms of typical endometriosis pain, such as dysmenorrhea, dyschezia, dysuria and/or dyspareunia. However, in the DE group, specific diaphragmatic pains such as upper right abdominal pain, shoulder pain, cyclic dyspnea, and cough were significantly more often present pre-operatively than in the group without DE (27.6% vs 1.8% p<.001). Of the 16 patients with shoulder pain, 13 (81.25%) underwent an MRI of the thorax; diaphragmatic lesions were detected in only 2 (15.3%) patients. Four patients (out of the 65) with resection of DE (6.1 %) were asymptomatic; in these cases, the indication for surgery was infertility and the patient had been consented for resection. Only one patient had a history of thoracic endometriosis. (Table 1).

Surgical treatment

All patients in the DE group were treated laparoscopically, as described above. In 42 of the 65 patients (64.6%), the patients' endometriotic lesions were excised; in 8 of the 65 cases (12.3%), they were evaporated by applying a CO2 laser. In 12 out of the 65 cases (18.5%), the DE was not removed because it was discovered incidentally during surgery for infertility; either the patients were asymptomatic, or there was no consent to a resection of diaphragmatic lesions. No complications during and after excising DE were noted. In our DE population specifically, no patient suffered postoperatively from phrenic nerve disorder.

Clinical implications and postoperative outcome of removing diaphragmatic endometriosis

Of the 32/65 women (49.2%) of DE population with preoperative infertility, 14/32 (43.7%) became pregnant postoperatively: 8/14 (57.1%) spontaneously, 6/14

(42.8%) with the support of reproductive medicine, and 8/32 (25%) did not conceive (with and without reproductive medicine).

In follow-up, 4/65 (6.2%) women underwent a second operation due to recurrence. All of these patients did not have DE recurrence; however, they opted for a definitive surgery with hysterectomy after an average of 6-10 years. 15/65 (23%) remained stably asymptomatic under prophylactic progesterone therapy. For 9/65 (13.8%) patients we have no postoperative information.

Discussion

In our study, DE was found in 4.7% of the endometriosis patients who were operated within the past 10 years for symptoms of endometriosis. In the current literature, the prevalence of DE is described as between 0.19% and 1.5% of all intra-abdominal lesions (4, 14, 35). The higher prevalence in our cohort is explained by the fact that at our institution all patients with suspicion of endometriosis undergo a complete laparoscopic inspection of the diaphragm bilaterally. Another explanation is that we are a specialized referral center treating patients with more severe endometriosis.

We did not observe a difference in the patients' ages between the DE patients and the patients with pelvic endometriosis only. Joseph et al. (15) and Nezhat et al. (1) noted a difference of 5 to 6 years in mean age between DE patients and patients with pelvic endometriosis only. Several authors describe this difference in age as due to a progression of pelvic endometriosis to DE (6, 4, 12). Another possible reason could be simply the delay of diagnosis of DE (15, 16, 17). The only explanation for the age difference is the extent of the standardized laparoscopic inspection of the diaphragm in each patient (38).

In our cohort, DE was often associated with severe endometriosis (rAFS III° or IV°) (78.4%). In 1998 Nezhat and in 2021 Ceccaroni reported that DE was found

primarily in women with severe pelvic endometriosis involving the bladder, ureter, and bowel (6, 16, 18, 4, 35, 45).

The high rate of severe endometriosis in our cohort could thus possibly also explain the significantly higher rate of infertility in the patients with DE (49.2%). This is in line with a previously published retrospective study showing a strong association between thoracic endometriosis and infertility (16). Unfortunately, it has for many years remained unclear whether the ASRM classification has any prognostic significance regarding prediction of a woman's fertility potential (27). According to Macer ML et al., women with mild endometriosis have been shown to have a significantly lower probability of pregnancy over 3 years than women with unexplained infertility (36% vs 55%, respectively) (28, 29). IVF studies have suggested that women with more advanced endometriosis have poor ovarian reserve, low oocyte and embryo quality, and poor implantation (28, 30, 33). The anatomic distribution of the lesions in the DE group showed more patients with the left lower pelvis affected. In cases of ovarian endometriosis, patients with DE showed a significantly higher prevalence of left ovaries involvement (left 63% vs right 35.7%, $p<.001$). This predisposition for endometriosis lesions of the left lateral ovarian tissues in patients with DE was also described by Vercellini. It is likely that the decreased fluid movements in the left pelvis due to the sigmoid colon probably caused the implantation of endometriotic cells on the left side (46). The diaphragm was affected on the right side in 92.3% of all DE cases; this is in line with Ceccaroni et al. (4), who found involvement of the right diaphragm in 80% of patients. This striking difference in the 2 sides and the distribution pattern of the endometriosis lesions in total suggest that the circulating peritoneal fluid transports the endometriosis cells to the right diaphragm; this supports the menstrual reflux theory referenced by Vercellini (6, 14, 19, 12, 17, 38). Independently of DE, it is known that

the left pelvic wall is more often affected, here possibly due to the anatomy of the sigmoid colon (46).

Even though the right diaphragm was affected in most patients, potentially resulting in phrenic nerve irritation that could provoke typical shoulder pain, shoulder pain was described in only 26% of the cases with DE in our cohort. Consistent with our observations are the results from Nezhat and Ceccaroni, who also reported the absence of cyclic shoulder pain. In the Nezhat cohort, 29% of patients reported shoulder pain; in the Ceccaroni cohort, 30%. Why some patients with DE develop local symptoms and others do not has not been determined to date (7). This is an issue to be studied in the future.

Classic endometriosis symptoms such as dysmenorrhea, dyschezia, dysuria, and/or dyspareunia were present in 90.8% of all patients with DE. The high rate of classic endometriosis symptoms in DE patients can be explained by the association of DE with severe pelvic endometriosis (4, 6, 16).

The absence of typical complaints associated with a diaphragmatic involvement makes the clinical diagnosis of DE very challenging. At our institution, we recommend a specific diaphragmatic MRI if a patient complains about cyclical shoulder pain, and if there is suspected or already proven pelvic endometriosis. This helps us improve the diagnostic pathway of DE and can generate further information preoperatively in order to optimize the intraoperative approach if a deep DE resection is indicated. Even though MRIs fail to detect small superficial nodules and small diaphragmatic lesions, they are sensitive to diaphragmatic lesions in about 80% in symptomatic DE patients (20, 21, 8). When performing an MRI, DE lesions are better seen on fat-suppressed T1-weighted sequences; T2-weighted sequences should also be produced to increase lesion detection (8).

If surgery is required, we perform laparoscopic surgery with the patient in a steep reverse Trendelenburg position, which allows for the detection of all DE lesions. We concur with Ceccaroni and Redwine: if sentinel lesions (endometriotic nodules of <1 cm in diameter located at the right anterior diaphragm) are found intraoperatively, examining the entire diaphragm is indispensable. Lesions that are located in a more posterior position may be hidden, yet may be associated with persistent or recurrent symptoms. Excision of the DE lesion should be the treatment of choice, but coagulation or even evaporization are also possible therapeutic options (Ceccaroni et al., 2013a) (Working group of ESGE, ESHRE, and WES et al.). However, coagulation of the DE lesions might be followed by complications such as diaphragm fenestrations, which were possibly the result of tissue necrosis caused by thermocoagulation after excision of deep endometriotic lesions (23). Using a CO2 laser for the vaporization of superficial lesions is favorable because of the smaller depth of penetration compared with electrocautery and because of better access to hard-to-reach areas (23, 24). According to the literature, radical excision of all lesions correlates with quality of life and fertility (22). Outcomes of surgery are found to be closely related to the experience of the surgeon (22, 43). Therefore, DE should be treated in a referral center by an expert laparoscopic gynecologist (4).

Phrenic nerve injury is a potential complication, a rare risk of which surgeons need to be aware (6, 11). In our cohort, no complications were registered peri-and postoperatively. Of course, every surgery must be well indicated; however, if surgery for endometriosis in general was indicated and the patient consented, an excision of DE should be performed in all patients with symptoms or infertility.

Strengths and Limitations

This is the first study looking systematically at the true prevalence of DE. Since the diaphragm was examined in a large cohort of patients, this study provides

valuable information on patients with DE. Another strength of our study is the prospective collection of data, although the data analysis was performed retrospectively. The principal limitations of our study are selection bias, since our department is an endometriosis referral center and the small number of patients with DE. An isolated posterior DE was not excluded if in the described diagnostic laparoscopy no DE was seen and no DE was suspected through imaging or symptoms. Also, the symptoms were not collected with a validated questionnaire.

Conclusion

Patients with shoulder pain, infertility and/or endometriosis in the left pelvis have a significant higher risk of DE and therefore need specific preoperative consulting and if indicated surgical treatment.

Precis

Patient with Diaphragmatic Endometriosis had endometriosis more often seen in the left lower pelvis, including ovarian involvement. These patients presented shoulder pain and showed a higher incidence of infertility.

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Legend

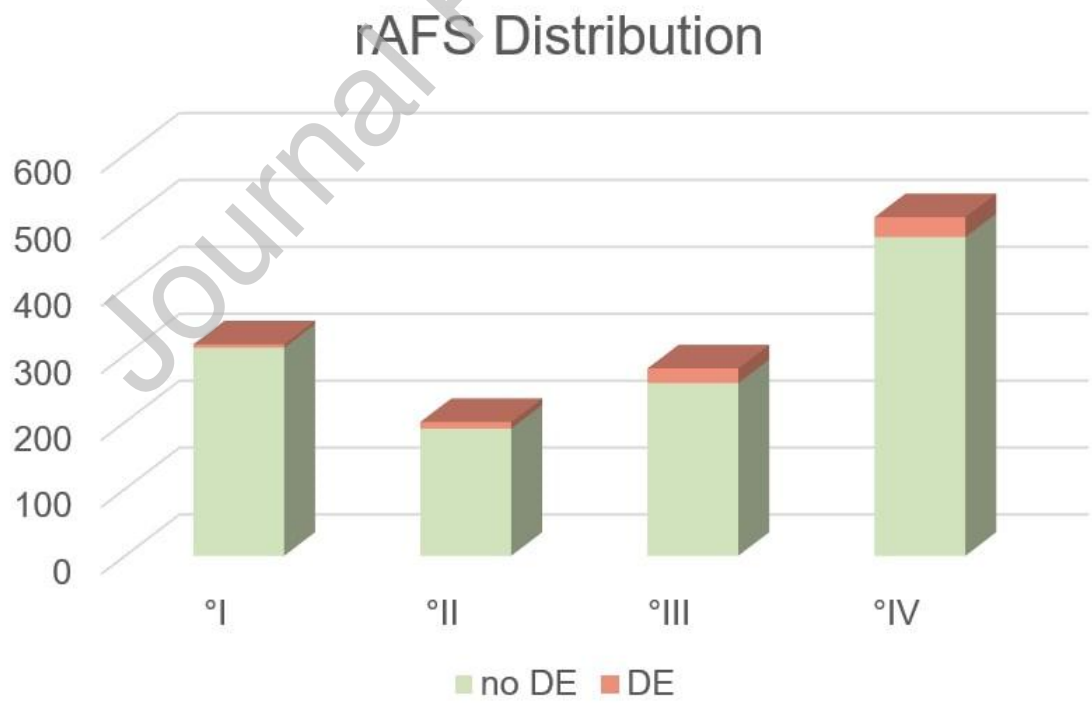

Figure 1. Comparison of endometriosis stages between the group of patients with diaphragmatic endometriosis (DE) and the group of patients with abdominal endometriosis without diaphragmatic involvement (no DE).

Table 1. Patient Characteristics

				DE		p-value
				yes	no	
				Patients N = 65	N = 1307	
Age, years, median (range)				34 (19-49)	33 (18-57)	
Indication for surgery, n (%)						
Diaphragm specific pain				18 (27.7%)	24 (1.8%)	<.001
Classic endometriosis symptoms (dysmenorrhea, dyschezia, dysuria)				59 (90.8%)	1125 (86.1%)	.404
Hematochezia				5 (7.7%)	3 (4.6%)	.274
Dyschezia				29 (44.6%)	430 (32.9%)	.007
Dysuria				15 (23.1%)	204 (15.6%)	.091
Dyspareunia				31 (47.7%)	618 (47.3%)	.526
Infertility				32 (49.2%)	375 (28.7%)	.000

rAFS stage, n (%)						
rAFS I				5 (7.7%)		
rAFS II				9 (13.8%)		
rAFS III				21 (32.3%)		
rAFS IV				30 (46.1%)		
rAFS III or IV				51 (78.4%)		.001
Compartment involvement						
Right Hemipelvis				66.1% (N =45)		
Left Hemipelvis				73.8% (N =48)		
Left ovary involvement				63% (N =41)		.001
Right ovary involvement				35.7% (N =23)		
both ovary involvement				15.3% (N = 10)		

Patient characteristics compared between DE and no DE

DE = diaphragmatic endometriosis; rAFS = revised American Fertility Society score

p-value: Chi square Cross Table