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Cycle-related Diarrhea and Dysmenorrhea are Independent Predictors of Peritoneal Endometriosis, Cycle-related Dyschezia is an Independent Predictor of Rectal Involvement

Zyklusabhängige Diarrhö und Dysmenorrhö sind unabhängige Prädiktoren für das Vorliegen einer peritonealen Endometriose, zyklusabhängige Dyschezie für das Vorliegen eines Rektumbefalls

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ABSTRACT

Introduction The clinical presentation of endometriosis is extremely varied. Because endometriosis symptoms may overlap with symptoms caused by gastroenterological disorders, this can lead to misdiagnosis and a considerable delay in arriving at the correct diagnosis. The aim was to evaluate the type and duration of endometriosis-related symptoms and to identify predictors for patterns of involvement depending on symptoms.

Material and Method The data of 266 consecutive patients who were operated on in the Endometriosis Center between 1/2016 and 12/2017 after receiving a histologically verified diagnosis of endometriosis were recorded. In addition to recording the clinical parameters, a questionnaire was distributed to the patients, who were asked about their medical history. Infertile patients were grouped together as Group 1 and compared to non-infertile patients (Group 2).

Results The response rate for returned questionnaires was 79.47 % (182/229). 41.8 % of patients reported that they were infertile and 91.8 % reported pelvic pain. In more than ⅓ of cases in both groups, more than 10 years passed between the initial symptoms and the final diagnosis (39.4 vs. 37.5 %). On average, patients consulted 2.72 (± 1.58) resp. 3.08 (± 1.72) doctors before they presented to a hospital or were referred for laparoscopic diagnostic workup ($p = 0.162$). Cycle-related diarrhea (odds ratio 2.707; 95 % CI: 1.063–6.895, $p = 0.037$) and dysmenorrhea (odds ratio 2.278; 95 % CI: 1.193–4.348, $p = 0.013$) were associated with involvement of the pelvic peritoneum, cycle-related dyschezia was associated with rectal involvement by a factor of 4.6 in binary regression analysis (odds ratio 4.659; 95 % CI: 1.132–19.186; $p = 0.033$).

Conclusion Cycle-related diarrhea and dysmenorrhea increase the risk probability of peritoneal endometriosis. Dyschezia increases the risk probability of rectal endometriosis.

ZUSAMMENFASSUNG

Einleitung Das klinische Erscheinungsbild der Endometriose ist vielfältig. Durch die mit gastroenterologischen Erkrankungen überlappenden Symptome kann es zu Fehldiagnosen und erheblicher Verzögerung der Diagnosestellung kommen. Ziel war es, die Art und Dauer der endometrioseassoziierten Symptome zu evaluieren sowie Prädiktoren für Befallsmuster in Abhängigkeit von den Beschwerden zu identifizieren.

Material und Methode Es erfolgte eine Erfassung von 266 konsekutiven Patientinnen, die im Zeitraum von 1/2016 bis 12/2017 aufgrund einer histologisch gesicherten Endometriose am Endometriosezentrum operiert wurden. Zusätzlich zur Erfassung klinischer Parameter wurden die Patientinnen über einen Fragebogen zu ihrer Krankengeschichte befragt. Patientinnen mit Sterilität wurden als Gruppe 1 den Patientinnen ohne Sterilität (Gruppe 2) gegenübergestellt.

Ergebnisse Die Rücksenderate der Fragebögen betrug 79,47% (182/229). 41,8% berichteten über eine Sterilität und 91,8% über Unterbauchschmerzen. Von Erstsymptom bis Diagnosestellung vergingen in beiden Gruppen in mehr als ⅓ der Fälle über 10 Jahre (39,4 vs. 37,5%). Bis zur Vorstellung in einer Klinik bzw. bis zur Indikation der laparoskopischen Diagnostik wurden im Mittel 2,72 (± 1,58) bzw. 3,08 (± 1,72) Ärzte aufgesucht (p = 0,162). Zyklusabhängige Diarrhö (Odds Ratio 2,707, 95%-KI 1,063–6,895, p = 0,037) und Dysmenorrhö (Odds Ratio 2,278, 95%-KI 1,193–4,348, p = 0,013) waren mit einem Befall des Beckenperitoneums assoziiert, die zyklusabhängige Dyschezie war mit dem Befall des Rektums um den Faktor 4,6 in der binären Regressionsanalyse assoziiert (Odds Ratio 4,659; 95%-KI 1,132–19,186; p = 0,033).

Schlussfolgerung Zyklusabhängige Diarrhö und Dysmenorrhö erhöhten das Risiko für das Vorhandensein einer peritonealen Endometriose. Dyschezie erhöhte das Risiko einer Rektumendometriose.

Introduction

Endometriosis is one of the most common, benign, gynecological disorders, affecting around 15% of all women of reproductive age, 60% of all women with chronic pelvic pain and 50% of all infertile women [1–3]. The incidence in Germany is 40 000 new cases per year; around 80 million women are affected worldwide [4–6]. The exact prevalence in the female population in the reproductive years is unknown as final confirmation is only possible with diagnostic laparoscopy. The most common sites of endometriosis include the pelvic peritoneum, the ovaries and the rectovaginal septum [7].

Endometriosis is a chronic disease which is associated with regular symptoms, repeated surgical interventions and lifelong hormone treatment. Long-term effects include chronic pain and infertility [7]. The clinical presentation of the disease is quite varied. Endometriosis may be asymptomatic and may only be detected as an incidental finding during abdominal surgery. As the symptoms are unspecific and they often overlap with the symptoms of other gynecological and gastroenterological disorders, misdiagnoses are common and can include irritable bowel syndrome or pelvic infection [8]. Symptoms typical for endometriosis include dysmenorrhea, pelvic pain, dyspareunia, dysuria and dyschezia as well as infertility [1, 9]. The heterogeneity of these symptoms makes it difficult to arrive at the correct diagnosis, which is often delayed. Despite the high incidence of endometriosis, on average 10.4 years elapsed between the initial symptoms and the final diagnosis. During this period, patients were given at least one incorrect diagnosis [10]. An international comparison showed similar figures for the interval between initial symptoms and correct diagnosis; in the USA, an average of 11.7 years elapsed and in Great Britain, the average was 8.0 years until the correct diagnosis was obtained [6, 9, 11, 12].

How much the patient is aware of the disease depends on the symptoms, when the correct diagnosis was made, and the patient's individual situation [13]. Receiving a diagnosis of endometriosis significantly affects the patient's health-related quality of life. The resilience of patients with endometriosis is reduced; on average, patients are off work 7.41 hours per week [14]. In the USA. the cost associated with treating endometriosis including the loss of working hours amounted to 69 billion dollars in 2009 [15, 16].

National and international consensus statements have been developed for the diagnosis and treatment of endometriosis. Non-invasive methods for a diagnostic workup include imaging procedures, the determination of serum biomarkers, and systematic questioning of patients about their symptoms [17, 18]. Out of a cohort of 1200 women who underwent laparoscopy for sterilization, infertility, pelvic pain or hysterectomy, patients in whom endometriosis was confirmed intraoperatively were significantly more often likely to have reported dysmenorrhea preoperatively [19]. Symptoms such as dyschezia and dyspareunia can be predictors for deep-infiltrating endometriosis [20]. An insufficient correlation between the extent of symptoms and the extensively used revised American Society of Reproductive Medicine (rASRM) classification of 1996 is being discussed internationally [21].

In this study, the aim was to evaluate the type and duration of endometriosis symptoms, the process of obtaining a diagnosis, and the relationship between the pattern of involvement and the symptoms based on a patient cohort from a well-established certified endometriosis center in Germany. The investigation looked at the clues provided by symptoms with the aim of improving sensitivity in future when taking patients' medical history and actively asking patients about their symptoms. When the individual areas were looked at, the subgroup of infertile patients were examined separately to determine possible differences in obtaining a diagnosis and the impact on the stage and subsequent course of disease.

Material and Methods

Study design and patient recruitment

The data of all patients who presented to the Clinic and Polyclinic for Gynecology and Reproductive Medicine at Jena University Hospital 1/2016 to 12/2017 to undergo surgery for endometriosis and its symptoms were retrospectively collected (n = 266). Patients were contacted by telephone and asked to complete and return a questionnaire. Patients with no histological confirmation of endometriosis were excluded from the study (n = 5).

Parameters such as age, prior pregnancies and attempts to have children, endometriosis stage using the rASRM and the ENZIAN classifications and the location of the endometriosis lesions were obtained from the electronic patient files. Preoperatively, patients underwent a gynecological examination with transvaginal ultrasound; if there was a suspicion of deep-infiltrating endometriosis, patients had additional examinations such as pelvic MRI, rectal endosonography and rectoscopy, cystoscopy, etc. Following surgery, endometriosis findings were staged ex post using the rASRM and the ENZIAN classification systems and the patterns of involvement detected intraoperatively. Surgical care included surgical steps such as cyst extirpation, excision and coagulation of endometriosis, adhesiolysis, ureterolysis with partial peritonectomy as well as bladder and bowel procedures, with the goal of completely removing all endometriosis lesions.

Research ethics approval and patient information and consent

Before starting the study, an application was sent to the ethics committee of Friedrich Schiller University Jena which approved the study (no. 5237-08/17). All patients gave their consent to the use of their clinical, anonymized data.

Questionnaire

To collect the data, a questionnaire was developed together with the Institute for Medical Statistics, Information Technology and Data Science. The questionnaire was designed to specifically obtain the following parameters: type and duration of symptoms before surgery, number of doctors consulted until the diagnosis was made, use of painkillers, how often patients were unable to work because of symptoms. The questionnaire was developed as part of a doctoral dissertation and was completed by the patients; their responses recorded in a database.

Statistical analysis

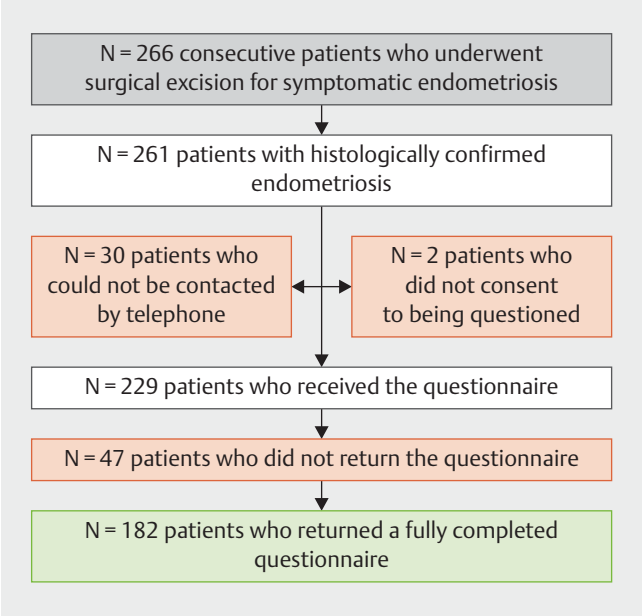
Statistical analysis was carried out using SPSS Version 25 (SPSS Inc., Chicago, IL, USA). Mean values and standard deviations or frequencies were calculated for continuous and categorical variables. Differences between mean values of metric variables were determined using Student's t-test and for categorical variables using Mann-Whitney U-test or Fisher's exact test. The patient population was divided into a group of patients with infertility (hereinafter referred to as Group 1; n = 76, 41.8%) and a group of patients without infertility (Group 2; n = 106, 58.2%). Multivariate, linear and binary regression analysis was used to investigate possible risk factors for the endometriosis stage or involvement based on preoperative symptoms.

A p-value of ≤ 0.05 was defined as statistically significant.

Results

Descriptive characteristics of the study population

The response rate for entirely completed questionnaires was 79.5% (182/229) (▶ **Fig. 1**). A total of 182 patients were treated for histologically confirmed endometriosis at the Clinic and Polyclinic for Gynecological and Reproductive Medicine of Jena University Hospital during the observation period and were available for questionnaire-based evaluation.



▶ **Fig. 1** Recruitment of the study population (recruited and contacted patients, n = 266) as a function of histological confirmation, return of the completed questionnaire (n = 229), and completeness of study data (n = 182).

41.8% (n = 76) of these patients reported a medical history of infertility. The percentage of primary diagnoses (71.1 vs. 69.8%, p = 0.871) und diagnoses of recurrence (28.9 vs. 29.2%, p = 1.0) was similarly distributed for both groups. Both patients with infertility and patients without infertility were diagnosed with endometriosis incidentally during other abdominal surgical procedures (5.3 vs. 5.7%; p = 1.0). On average, patients with infertility were significantly younger (32.84 ± 6.18 years) compared to patients without infertility (35.28 ± 9.75 years) (p = 0.041).

Symptom-related parameters

Patients reported chronic pelvic pain as the most common symptom with 91.8%. In decreasing order, other reported symptoms were dyspareunia (53.3%), dysmenorrhea (47.3%), dyschezia (46.7%) and dysuria (24.7%). A group-specific examination of symptoms, summarized in ▶ **Table 1**, shows that patients without infertility reported dyschezia significantly more often compared to patients with infertility (53.8 vs. 36.8%, p = 0.035).

In addition to dyschezia, patients were asked about the frequency of unspecific, cycle-related abdominal complaints. Patients in Group 2 reported a feeling of abdominal pressure (12.3 vs. 1.3%, p = 0.009), diarrhea (31.1 vs. 13.2%, p = 0.005) and constipation (21.7 vs. 9.2%, p = 0.027) significantly more often than patients in Group 1. No group-specific distribution was found for hematochezia (14.2 vs. 9.2%, p = 0.36) and flatulence (13.2 vs. 9.2%, p = 0.485).

Another aspect recorded in the questionnaire was the frequency of symptoms. Patients in Group 2 reported that symp-

▶ **Table 1** Endometriosis-specific symptoms reported by the study population; results are presented as absolute values and percentages.

Symptom-related parameters	Group 1: endometriosis patients with infertility n = 76	Group 2: endometriosis patients without infertility n = 106	p-value
Dysmenorrhea	35 (46.1%)	51 (48.1%)	0.08
Pelvic pain	68 (89.5%)	99 (93.4%)	0.42
Dyspareunia	35 (46.1%)	62 (58.5%)	0.10
Dysuria	16 (27.4%)	29 (21.1%)	0.39
Dyschezia	28 (36.8%)	57 (53.8%)	**0.03**

▶ **Table 2** Symptom-related parameters of the study population such as frequency of symptoms, regular use of painkillers and frequency of having to take time off work; results are presented as absolute values and percentages.

Symptom-related parameters	Group 1: endometriosis patients with infertility n = 76	Group 2: endometriosis patients without infertility n = 106	p-value
Frequency of symptoms	59 (77.6%)	96 (90.6%)	**0.020**
▪ every day	5 (6.6%)	16 (15.1%)	
▪ every week	3 (3.9%)	6 (5.7%)	
▪ every month	50 (65.8%)	74 (69.8%)	
Regular use of painkillers	50 (65.8%)	84 (79.2%)	0.060
▪ every day	3 (3.9%)	8 (7.5%)	
▪ every week	4 (5.3%)	8 (7.5%)	
▪ every month	43 (56.6%)	68 (64.2%)	
Frequency of having to take time off work			0.203
▪ every week	0 (0%)	1 (0.9%)	
▪ every month	6 (7.9%)	17 (16.0%)	
▪ every year	2 (2.6%)	1 (0.9%)	

toms occurred regularly significantly more often compared to patients with infertility (90.6 vs. 77.6%, p = 0.02), with symptoms usually occurring at monthly intervals (69.8 vs. 65.8%). Both groups of patients reported having to take time off work because of symptoms, usually in monthly intervals (10.5 vs. 17.9%; p = 0.159). ▶ **Table 2** summarizes the distribution of symptom-related parameters.

Diagnosis-related parameters

In ⅓ of cases in both groups, more than 10 years elapsed between the first emergence of symptoms and the diagnosis of endometriosis (39.4 vs. 37.5%). Patients who were also infertile (Group 1) consulted 2.72 (± 1.58) doctors on average until the diagnosis of endometriosis was made, patients without infertility (Group 2) consulted an average of 3.08 (± 1.72) different doctors (p = 0.162). Patients in both groups reported a positive familial history of endometriosis (13.2 vs. 18.9%, p = 0.418). ▶ **Table 3** summarizes the diagnosis-related parameters.

Endometriosis-related parameters:

There were no group-specific differences in rASRM stage distribution. Of the patients in Group 1, 26.4% (n = 19) were classified as rASRM stage I, 25% (n = 18) as rASRM stage II, 19.4% (n = 14) as rASRM stage III and, the most common finding, 29.2% (n = 21) were classified as rASRM stage IV. The most common classification of patients in Group 2 was rASRM stage I (28.3%, n = 28), followed by rASRM stage II in 22.2% of cases (n = 22), rASRM stage III in 23.2% (n = 23) and rASRM stage IV in 26.3% (n = 26). In both groups, the most common classification of patients with deep infiltrating endometriosis was ENZIAN B (31 vs. 47, p = 0.53). The distribution of stages is shown below in ▶ **Table 4**.

In our patient population, linear multivariate regression analysis showed no significant increase in the probable risk of higher grade rASRM scores as a function of typical symptoms such as "dysmenorrhea", "pelvic pain", "dyspareunia", "dysuria", "dyschezia" and "infertility". The results are summarized in ▶ **Table 5**. When the pattern of involvement was evaluated, the most common location in both groups of patients was the pelvic peritone-

▶ **Table 3** Diagnosis-related parameters of the study population such as time to diagnosis, type of diagnosis, familial history and number of doctors consulted until the diagnosis of endometriosis was made; results are presented as absolute values and percentages.

Diagnosis-related parameters	Group 1: endometriosis patients with infertility n = 76	Group 2: endometriosis patients without infertility n = 106	p-value
Time to diagnosis			0,69
▪ < 1 year	12 (16.9%)	14 (13.5%)	
▪ 1–5 years	22 (31.0%)	31 (29.8%)	
▪ 6–10 years	9 (12.7%)	20 (19.2%)	
▪ > 10 years	28 (39.4%)	39 (37.5%)	
Primary diagnosis	54 (71.1%)	74 (69.8%)	0.87
Diagnosis of recurrence	22 (28.9%)	31 (29.2%)	1.00
Incidental diagnosis	4 (5.3%)	6 (5.7%)	1.00
Positive familial history	10 (13.2%)	20 (18.9%)	0.42
Number of doctors consulted until the diagnosis was made	2.72 ± 1.58	3.08 ± 1.72	0.16
▪ 1	13 (17.1%)	11 (10.4%)	0.24
▪ 2	31 (40.8%)	43 (40.6%)	
▪ 3	15 (19.7%)	20 (18.9%)	
▪ 4	8 (10.5%)	12 (11.3%)	
▪ 5	5 (6.6%)	9 (8.5%)	
▪ > 5	2 (2.6%)	13 (13.0%)	

um (43 vs. 60, p = 1.0). Binary regression analysis showed a significant increase in the probable risk of involvement of the pelvic peritoneum as a function of the symptoms; according to this analysis, dysmenorrhea increased the risk 2.3-fold (p = 0.013). The occurrence of dyspareunia decreased the risk of pelvic peritoneum involvement (odds ratio 0.475, p = 0.037). The results are summarized in ▶ **Table 6**. No significant increases in probable risk based on the symptoms "dysmenorrhea", "pelvic pain", "dyspareunia", "dysuria", "dyschezia" and "infertility" were detected for compartments A, B and C of the ENZIAN classification.

In binary regression analysis, the risk probability for involvement of the pelvic peritoneum for unspecific but cycle-related gastrointestinal symptoms such as dyschezia, hematochezia, feeling of abdominal pressure, diarrhea, constipation, bloating and pelvic pain was significantly higher, with a 2.7-fold increase if patients reported a history of cycle-related diarrhea (odds ratio: 2.707, 95% CI: 1.063–6.895, p = 0.037). Moreover, analysis of these unspecific cycle-related gastrointestinal complaints found a significant 4.6-fold increase in the risk probability for rectal involvement if patients reported cycle-related dyschezia (odds ratio: 4.659, 95% CI: 1.132–19.186, p = 0,033).

Fertility-related parameters

There was a high percentage of nulligravida in the group with infertility (53.9%) compared to Group 2 (46.2%) (p = 0.046). Patients with infertility reported significantly lower numbers of spontaneous conceptions in previous pregnancies (34.2 vs. 49.1%, p = 0.05) and a significantly higher number had used ART (31.6 vs. 6.6%, p = 0.001).

Therapy-related parameters

Following surgical excision, the percentage of patients who returned to work was similar in both groups. The majority of patients had fully returned to work at two months postoperatively (94.7 vs. 93.4%, p = 0.413). The reported severity of pain measured using the visual analog pain scale decreased significantly in both groups postoperatively (from 7.05 to 2.57 vs. 7.37 to 2.28).

The majority of patients in both groups felt that endometriosis impaired their quality of life (64.5 vs. 78.3%); this was even more pronounced in Group 2 (p = 0.045).

Discussion

This study aimed to evaluate the type and duration of endometriosis complaints in a patient population which presented to a clinical-scientific endometriosis center. The study also investigated the effect of the pattern of endometriosis involvement on specific complaints.

The mean age of the investigated patient population was 34.26 years, and infertility was reported by 41.8% of cases. Pelvic pain was the most commonly reported symptom (91.8%). Peterson et al. investigated risk factors for the presence of endometriosis in 473 patients prior to laparoscopy; the risk probability of detecting endometriosis intraoperatively increased 3.6-fold if patients reported pelvic pain (OR 3.67, 95% CI: 2.44–5.50) and 2.4-fold if they reported dysmenorrhea (OR 2.46; 95% CI: 1.28–4.72). In addition to specific symptoms such as pelvic pain, dysmenorrhea, dyspareunia, dyschezia and dysuria, patients with endometriosis also reported unspecific gastrointestinal complaints

▶ **Table 4** Stage-related parameters of endometriosis involvement in the study population using the ENZIAN and the rASRM (classification of the American Society for Reproductive Medicine) classification systems; results are presented as absolute values and percentages.

Endometriosis-related parameters	Group 1: endometriosis patients with infertility n = 76	Group 2: endometriosis patients without infertility n = 106	p-value
rASRM score			0.90
▪ I	19 (26.4%)	28 (26.4%)	
▪ II	18 (25%)	22 (20.6%)	
▪ III	14 (19.4%)	23 (21.7%)	
▪ IV	21 (29.2%)	26 (24.5%)	
ENZIAN classification			
A compartment	11 (14.5%)	11 (10.3%)	1.00
▪ A1	3 (3.9%)	3 (2.8%)	
▪ A2	4 (5.3%)	4 (3.8%)	
▪ A3	4 (5.3%)	4 (3.8%	
B compartment	31 (40.8%)	47 (44.3%)	0.53
▪ B1	5 (6.6%)	13 (12.3%)	
▪ B2	18 (23.7%)	24 (22.6%)	
▪ B3	8 (10.5%)	10 (9.4%)	
C compartment	14 (18.4%)	16 (15.1%)	0.52
▪ C1	6 (7.9%)	7 (6.6%)	
▪ C2	5 (6.6%)	3 (2.8%)	
▪ C3	3 (3.9%)	6 (5.6%)	
▪ FA	1 (1.3%)	1 (0.9%)	1.0
▪ FB	2 (2.6%)	2 (1.8%)	1.0
▪ FI	4 (5.3%)	5 (4.7%)	1.0
▪ F0	2 (2.6%)	6 (5.6%)	0.47

▶ **Table 5** Results of linear multivariate regression analysis to evaluate risk factors for rASRM stages of endometriosis involvement as a function of specific symptoms reported by the study population.

Symptom	Regression coefficient B	SE	p-value	Lower CI	Upper CI
Dysmenorrhea	0.054	0.180	0.766	− 0.302	0.409
Pelvic pain	0.445	0.324	0.172	− 0.196	1.086
Dyspareunia	− 0.331	0.196	0.094	− 0.719	0.057
Dysuria	− 0.163	0.222	0.464	− 0.600	0.275
Dyschezia	0.294	0.201	0.145	− 0.103	0.691
infertility	0.051	0.184	0.782	− 0.312	0.414

CI = confidence interval, B is the calculated regression coefficient, SE is the standard error of the regression coefficient.

▶ **Table 6** Results of binary regression analysis to evaluate risk factors for endometriosis involvement of the pelvic peritoneum as a function of specific symptoms reported by the study population.

Symptom	Regression coefficient B	SE	p-value	Odds ratio	Lower CI	Upper CI
Dysmenorrhea	0.823	0.33	**0.013**	2.278	1.193	4.348
Pelvic pain	0.249	0.586	0.670	1.283	0.407	4.043
Dyspareunia	− 0.745	0.356	**0.037**	0.475	0.236	0.954
Dysuria	0.671	0.411	0.103	1.956	0.874	4.376
Dyschezia	− 0.353	0.357	0.322	0.702	0.349	1.414
Infertility	− 0.083	0.331	0.801	0.920	0.481	1.760

CI = confidence interval, B is the calculated regression coefficient, SE is the standard error of the regression coefficient.

[8]. A group-specific examination of symptoms showed that patients without infertility were particularly likely to report dyschezia (p = 0.035) and unspecific, cycle-related gastrointestinal symptoms such as a feeling of abdominal pressure (p = 0.009), diarrhea (p = 0.005) and constipation (p = 0.027). The overlap of endometriosis symptoms with symptoms of gastroenterological disorders made obtaining the correct diagnosis more difficult, not least because of misdiagnoses, particularly among patients without infertility. In a study by Seaman et al. which examined 5540 patients with endometriosis, patients with endometriosis received a diagnosis of irritable bowel syndrome 3.5 times more often (OR 3.5; 95% CI: 3.1–3.9) compared to patients without endometriosis. The issue of bowel involvement in endometriosis is controversially discussed in the literature. The majority of endometriosis lesions are in the area of the pelvic peritoneum in the immediate vicinity of terminal sections of the large intestine. The inflammation-related irritation and release of prostaglandins could explain the reported disorders of bowel function [22]. Binary regression analysis showed a 2.7-fold increase in the risk probability of involvement of the pelvic peritoneum as a function of these unspecific cycle-related gastrointestinal complaints (dyschezia, hematochezia, feeling of abdominal pressure, diarrhea, constipation, bloating and pelvic pain) if patients had previously reported cycle-related diarrhea (p = 0.037, odds ratio 2.707, 95% CI: 1.063–6.895).

Hudelist et al. showed that patients with endometriosis had a history of at least one misdiagnosis. In addition to misdiagnoses which can be a consequence of symptoms which overlap with those of gastroenterological disorders, unspecific complaints also lead to a delay in obtaining the correct diagnosis [10]. Ballard et al. found that in addition to patients being misdiagnosed, symptoms were played down and/or suppressed by taking oral, hormone-based contraceptives and that diagnostic tests with a low sensitivity and specificity were often used [23]. In almost 40% of cases of the total patient population, more than 10 years passed (39.4 vs. 37.5%) between experiencing the initial symptoms and obtaining the correct diagnosis; no differences were found between patients with infertility and patients without infertility (p = 0.699). Overall, however, the percentage of diagnoses obtained within the space of less than one year was somewhat higher in the group of patients with infertility (16.9 vs. 13.5%). With regard to the time to diagnosis, patients with infertility appear to benefit from the surgical diagnostic workup for infertility. Hudelist et al. reported a delay of 10.4 years in Germany and Austria in obtaining the correct diagnosis for 171 patients [10]. An international comparison of the time to diagnosis showed that figures ranged from 11.7 years (USA) to 6.7 years (Norway) [8]. Patients regularly report that symptoms have been present for 180 months and that the time to diagnosis was delayed by 102 months [23]. In our patient population, patients consulted 2.93 ± 1.672 doctors on average until they obtained the final diagnosis. There was no significant difference between groups of women with and without infertility (2.72 ± 1.58 vs. 3.08 ± 1.72, p = 0.162).

As regards the distribution of rASRM stages, stages I–IV were evenly distributed (25.8%, 22.0%, 20.3%, 25.8%). However, because of the retrospective study design, it was not possible to differentiate between endometriosis lesions and endometriosis-related adhesions. No significant differences in the distribution of rASRM stages were found between the two groups (p = 0.9). As regards the typical symptoms of dysmenorrhea, pelvic pain, dyspareunia, dysuria, dyschezia and infertility, linear multivariate regression analysis found no significant increase in risk probability for higher rASRM scores. Other studies have already demonstrated a lack of correlation between rASRM scores and the severity of patients' complaints [21]. The strength of the rASRM classification system is the international prevalence and acceptance of the system and its ease of use [24]. It should be noted that this classification system does not take deep infiltrating endometriosis into account.

Deep infiltration is found in 48% of all endometriosis cases; these findings are associated with more pronounced symptoms than superficial endometriosis [25]. In the patient population studied here, a total of 152 lesions were classified as deep infiltrating endometriosis using the ENZIAN classification. An ENZIAN B score was the most common ENZIAN classification in both groups (31 vs. 47, p = 0.53). The low incidence of uterine adenomyosis in our patient population was due to the difficulty of histologically confirming uterine adenomyosis without uterine resection and the low rate of hysterectomies performed in our patient population. Haas et al. studied 194 cases and found that, in contrast to the rASRM score, the ENZIAN classification showed a correlation with clinical symptoms. Findings in compartment A showed a

strong association with pelvic pain (p = 0.012), findings in compartment C were associated with gastrointestinal complaints (p = 0.011) [26]. In our study, binary regression analysis of cycle-related gastrointestinal complaints such as dyschezia, hematochezia, feeling of abdominal pressure, diarrhea, constipation, bloating and pelvic pain showed a significant 4.6-fold increase in the risk probability for compartment C involvement if patients reported dyschezia (p = 0.033, odds ratio 4.659, 95% CI: 1.132–19.186).

Another strength of the ENZIAN classification system is the attribution to a specific organ or compartment. The most common pattern of involvement for both groups of patients was the pelvic peritoneum (43 vs. 60, p = 1.0) and the ovaries (34 vs. 45, p = 0.87). Binary regression analysis showed a significantly increased risk for involvement of the pelvic peritoneum based on reported symptoms; according to this analysis, dysmenorrhea increased the risk of pelvic peritoneum involvement 2.3-fold (p = 0.013). The occurrence of dyspareunia decreased the risk of pelvic peritoneum involvement (odds ratio 0.475, p = 0.037). Some studies have suggested that deep dyspareunia may be associated with deep infiltrating endometriosis [27].

The heterogeneity of endometriosis symptoms delays the diagnosis and makes obtaining a correct diagnosis more difficult [28]. rASRM scores are not correlated with patients' symptoms. In addition to typical symptoms such as dysmenorrhea, symptoms such as unspecific cycle-related gastrointestinal complaints such as diarrhea can be indications pointing to a diagnosis of peritoneal endometriosis. Such symptoms can be investigated safely and with few complications early on, using minimally invasive surgery, which could prevent misdiagnoses such as irritable bowel syndrome. Symptoms such as dyschezia can be an indication of deep infiltrating endometriosis with involvement of the rectum. Patients with endometriosis and infertility have a higher percentage of diagnoses made within the space of less than one year and need to consult fewer doctors on average until they obtain the correct diagnosis; overall, however there were no differences between the two patient cohorts which could be useful in clinical practice to improve the diagnostic workup.

Conclusion

In almost 40% of our total patient population, more than 10 years passed between experiencing the first symptoms to obtaining the correct diagnosis. To reduce the delay in obtaining a correct diagnosis, physicians should actively ask about typical endometriosis symptoms and be aware that unspecific cycle-related gastrointestinal complaints in young women of reproductive age can be indications for endometriosis. Unspecific, cycle-related gastrointestinal complaints such as diarrhea and dysmenorrhea increase the risk probability for peritoneal endometriosis. Cycle-related dyschezia increases the risk probability for rectal endometriosis. The use of diagnostic laparoscopy as a minimally-invasive diagnostic procedure can reduce the delay in obtaining the correct diagnosis, particularly if used in combination with targeted taking of the patient's history and careful questioning about symptoms.

Conflict of Interest

The authors declare that they have no conflict of interest.

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