GENERAL GYNECOLOGY

Unexpected coexistent endometriosis in women with symptomatic uterine leiomyomas is independently associated with infertility, nulliparity and minor myoma size

Kristin Nicolaus[1] · Dominik Bräuer[1] · Robert Sczesny[1] · Thomas Lehmann[2] · Herbert Diebolder[1] ·
Ingo B. Runnebaum[1]

Abstract

Purpose To determine risk factors for unexpected coexistent endometriosis in laparoscopic myomectomy for symptomatic uterine leiomyomas.

Methods This was a single-centre, retrospective cohort study conducted at a University Women's Hospital with a certified endometriosis centre. Data were collected from patients with symptomatic uterine leiomyomas who underwent laparoscopic myomectomy. The main outcome measured in the study was the presence of histologically confirmed endometriosis. Binary regression analysis was used to investigate risk factors for the coexistence of endometriosis. Postoperative complications were classified according to the Clavien–Dindo classification.

Results From 2014 to 2018, 223 patients underwent laparoscopic myomectomy for symptomatic leiomyomas, and 57 (25.6%) had unexpected endometriosis. Women with endometriosis significantly more frequently were nulliparous (66.7% vs. 51.2%; $p = 0.04$), had reported infertility (31.6% vs. 15.7%; $p = 0.01$) and smaller leiomyomas (mean diameter 4.92 cm) than women without endometriosis (mean diameter 6.02 cm; $p = 0.006$). Coexistent endometriosis significantly increased mean operative time (168.4 vs. 142.8 min; $p = 0.05$) while intra- and postoperative complications showed a similar distribution ($p = 0.87$) and length of hospital stay ($p = 0.26$). Binary regression analysis identified 2.3- and 2.2-fold increases in the risk of endometriosis for infertility ($p = 0.042$) and nulliparity ($p = 0.041$), respectively. Myoma size influenced the risk of endometriosis by a factor of 0.8 per cm ($p = 0.037$).

Conclusions Coexistent endometriosis should be expected in leiomyoma patients particularly with nulliparity, infertility or minor myoma size as independent risk factors. Preoperative counselling should incorporate surgical therapy of coexisting endometriosis.

Keywords Coexistent endometriosis · Laparoscopic myomectomy · Symptomatic uterine leiomyoma · Clavien–Dindo classification

Introduction

Endometriosis and uterine leiomyomas are exceedingly common gynaecological disorders. Leiomyomas are the most common benign gynaecological tumours, affecting 20–25% of women of reproductive age [1–3], particularly in infertility cases [4]. Our group and others have shown that myomectomy can improve fertility and pregnancy outcomes, and 5-year relapse rate is low with 21% and leads to long-term patient satisfaction, also in peri- and postmenopausal women [5–8]. Up to 50% of myomas are symptomatic and the symptoms depend on the number, size and location of

✉ Ingo B. Runnebaum
direktion-gyn@med.uni-jena.de

1 Department of Gynecology and Reproductive Medicine, University Women's Hospital Jena, Jena University Hospital, Friedrich-Schiller-University Jena, Am Klinikum 1, 07747 Jena, Germany

2 Institute of Medical Statistics, Informatics and Documentation, Jena University Hospital, Friedrich-Schiller-University Jena, 07747 Jena, Germany

the myomas. Symptoms include abnormal bleeding, pelvic pain and pelvic pressure leading to treatment [2, 3, 9].

Endometriosis occurs in 10–15% of women of reproductive age and is more frequent in infertile women, where it occurs in 25–40% [10]. The most common symptoms are chronic pelvic pain, dyspareunia, dysmenorrhea and subfertility. The gold standard for the diagnosis of endometriosis, especially for peritoneal endometriosis is the laparoscopy with biopsy [11]. Due to the overlap of symptoms shared by endometriosis and uterine leiomyomas, it may be difficult to find the accurate diagnosis without imaging. However, myomas are easily diagnosed via ultrasound or magnetic resonance imaging (MRI) and, therefore, myomas are commonly the indication for surgical intervention [11]. The diagnosis of endometriosis during surgical intervention for myomas can extend the operation time and the level of intra- and postoperative complications because of additional surgical procedures.

The presence of unexpected coexistent endometriosis in patients with uterine fibroids is poorly understood. New evidence from the first genome-wide association study (GWAS) on the genetic background of leiomyoma revealed risk loci shared by endometriosis conceivably leading to development and oestrogen-dependent growth [12]. Variants associating with uterine leiomyoma highlight genetic background shared by various cancers and hormone-related traits [12].

This study was to evaluate the prevalence and risk factors of unexpected coexistent endometriosis in women undergoing laparoscopic myomectomy.

Materials and methods

All data for patients who underwent a uterus-preserving laparoscopic myomectomy to treat symptomatic leiomyomas without a previous diagnosis of endometriosis at our department between January 2014 and December 2018 were retrospectively included in the study ($N=223$). Open procedures and cases with surgical treatment of submucous myomas were excluded from this study.

Patients reporting menorrhagia or irregular bleeding underwent diagnostic/operative hysteroscopy before myomectomy. All patients with infertility had chromopertubation performed at the time of surgery. The presence of endometriosis was defined by visualisation of endometriotic lesions during laparoscopy and histopathologic diagnosis. All patients in the present study underwent excision and histopathologic confirmation of endometriotic lesions rather than coagulation and destruction.

All patients were assessed preoperatively when the symptoms and the baseline items were recorded. Patients underwent preoperative mapping of myomas by transvaginal and transabdominal ultrasound and, in special cases, patients received an additional MRI. Uterine size and the number and location of leiomyomas were recorded. Patients with known endometriosis were excluded. By systematic file inspection, parameters such as age at the time of surgery, parity, previous abdominal operations, date and duration of the surgery, conversion to laparotomy, surgical procedures, endometriosis stages according to revised American Society for Reproductive Medicine rASRM [13], histological findings, length of hospital stay, intra- and postoperative complications, as well as progress information were taken from clinical documentation and the medical reports of patients 3 months after surgery. Postoperative complications include any deviations from the perioperative standard for prescribed medication, blood transfusion and/or secondary surgery during the inpatient stay and 48 h thereafter. These parameters were classified as grades I–V according to the Clavien–Dindo classification.

The statistical analysis was performed with SPSS v25 (SPSS Inc., Chicago IL USA). Comparisons of continuous data between the two groups were performed with non-parametric Mann–Whitney U test or the parametric unpaired t test according to the data distribution. Mean $\pm$ SD values are presented to describe the data for each group. Fisher's exact test was applied to compare categorical data between the groups, and absolute and relative frequencies are reported for both groups. A binary regression analysis was performed to determine the risk factors for coexistent endometriosis. A p value ≤ 0.05 was defined as statistically significant.

This research project was covered by the study approval for data use and clinical studies of the General Ethics Commission, Faculty of Medicine, Jena University Hospital, Germany (no. 2019-1314). An additional ethical approval from the Ethics Commission of the Faculty of Medicine, Jena University Hospital, Germany, was not required because the analysed data were anonymised. Statement on consent for participation from participants was obtained.

Results

In the period from 01/2014 to 12/2018, a total of 223 patients were included fitting the inclusion and exclusion criteria for further evaluation of endometriosis in laparoscopic myomectomy. The mean (SD) age of the study population was 40.3 (7.9) years and body mass index (BMI) was 24.7 (4.8).

Of the 223 patients, 57 (25.6%) had endometriosis and 166 (74.4%) did not. Baseline characteristics are given in Table 1. There was no statistically significant difference in age, BMI, age of menarche and menstrual cycle length between the two groups. Women with endometriosis were significantly more often nulliparous (66.7%) compared to women without endometriosis (51.2%) ($p=0.04$) and

Table 1 Patient baseline characteristics of the study population

Variable	Patients with endometriosis ($n=55$)	Patients without endometriosis ($n=166$)	Mean difference	95% CI	p value
Age, years	40.42 (6.7)	40.27 (8.3)	−0.15	−2.57 to 2.27	0.89
BMI, kg/m²	24.37 (4.2)	24.90 (5.0)	0.52	−0.83 to 1.88	0.48
Nulliparity	66.7	51.2	1.30	−1.03 to 1.65	**0.04**
Menarche, years	13.63 (1.2)	13.72 (1.4)	0.09	−0.31 to 0.49	0.65
Menstrual cycle length, days	27.35 (4.4)	28.43 (6.3)	1.08	−0.71 to 2.87	0.23
Cigarettes per day	0.46 (2.2)	1.37 (4.3)	0.91	−0.27 to 2.11	**0.04**
Symptoms					
Bleeding	42.1	50.0	0.84	0.59 to 1.19	0.35
Pain	29.8	38.6	0.77	0.49 to 1.21	0.27
Dysmenorrhea	28.1	25.9	1.08	0.66 to 1.77	0.73
Infertility	31.6	15.7	2.02	1.19 to 3.40	**0.01**

p values < 0.05 are in bold

Data are presented as mean ± standard deviation or as percentage, analysed using the Fisher exact test

CI confidence interval, *RR* relative risk

smoked fewer cigarettes (0.46/day) than women without endometriosis (1.3/day; $p=0.04$). Women with endometriosis reported symptoms such as bleeding disorders, pain and dysmenorrhea with similar frequencies and the difference between the two groups was not statistically significant. Infertility was significantly more common in patients with leiomyomas and coexistent endometriosis (31.6% vs. 15.7%; $p=0.01$). Women with myomas and endometriosis had undergone similar numbers of surgical uterine interventions in the past, such as curettage and artificial abortion (11.1% vs. 24.7%) and abdominal caesarean (8.8% vs. 8.4%) than women without endometriosis ($p=0.84$ and $p=0.08$).

Surgical and pathologic findings are given in Table 2. Women with leiomyomas and simultaneous endometriosis had smaller myomas (mean diameter 4.92 cm) than women without endometriosis (mean diameter 6.02 cm; $p=0.006$). Number of leiomyomas, weight and locations had no

influence on the prevalence of endometriosis. Women with coexistent endometriosis had endometriotic lesions in the peritoneum of the lesser pelvis (75.4%), uterosacral ligament (26.3%), ovaries (12.3%) and uterus (8.8%). Endometriosis was diagnosed at rASRM stages I (29.8%), II (29.8%), III (12.3%) and IV (10.4%). In 17.6%, even deep infiltrating endometriosis was detected.

Perioperative outcomes are given in Table 3. Coexistent endometriosis increased surgery time significantly (168.4 vs. 142.8 min; $p=0.05$). Intra- and postoperative complications showed a similar distribution ($p=0.87$), as did the length of hospital stay (0.26). Grade-III complications comprised six events (intraoperative bowel injury, postoperative bleeding and infected hematoma) and were treated surgically. There were no Grade-IV or -V complications.

In the binary regression analysis (Table 4) to determine the relative risk of coexistent endometriosis, 2.3- and

Table 2 Myoma baseline characteristics of the study group

Variable	Patients with endometriosis ($n=55$)	Patients without endometriosis ($n=166$)	Mean difference	95% CI	p value
Myoma size, cm	4.92 (2.37)	6.02 (2.65)	1.10	0.32 to 1.88	**0.006**
No. of myomas	1.86 (1.84)	2.05 (2.14)	0.19	−0.43 to 0.82	0.54
Myoma weight, g	121.25 (216.72)	169.30 (217.53)	48.06	−17.69 to 113.81	0.15
Location of myoma					0.22
Intramural	59.6	58.4			
Subserous	31.6	24.1			
Intramural and subserous	8.8	17.5			

p value < 0.05 is in bold

Data are presented as mean ± standard deviation or as percentage, analysed using the Fisher exact test

CI confidence interval

Table 3 Surgical and postoperative parameters for the study group

Variable	Patients with endometriosis ($n=55$)	Patients without endometriosis ($n=166$)	Mean difference	95% CI	p value
Operative time, min	168.47 (94.88)	142.80 (83.07)	−25.67	−51.75 to 0.41	**0.05**
Complications					0.87
CD I	87.7	83.7			
CD II	10.5	13.3			
CD III	1.8	3.0			
Length of stay, days	4.63 (1.75)	4.38 (1.37)	−0.25	−0.69 to 0.19	0.26

p value < 0.05 is in bold

Data are presented as mean ± standard deviation or as percentage, analysed using the Fisher exact test

CI confidence interval

Table 4 Binary regression analysis to determine the risk factors for the coexistent endometriosis in the study group

	Regression coefficient B	Standard error	p value	Odds ratio	Lower CI	Upper CI
Age	0.048	0.025	0.06	1.05	0.998	1.102
BMI	−0.026	0.035	0.459	0.974	0.910	1.044
Smoking (cigarettes/day)	−0.076	0.060	0.207	0.927	0.823	1.043
Symptom: pain						
Yes vs. no	0.112	0.277	0.686	1.119	0.649	1.926
Symptom: bleeding						
Yes vs. no	0.140	0.357	0.695	1.150	0.572	2.314
Symptom: dysmenorrhea						
Yes vs. no	−0.368	0.393	0.349	0.692	0.321	1.495
Symptom: infertility						
No vs. yes	0.829	0.408	**0.042**	2.292	1.030	5.101
No. of myomas	−0.044	0.098	0.653	0.957	0.790	1.160
Myoma size	−0.181	0.087	**0.037**	0.835	0.704	0.989
Location of myomas—intramural vs. subserous vs. both	−0.149	0.256	0.562	0.862	0.521	1.424
Weight of myomas	0.000	0.001	0.864	1.000	0.998	1.003
Nulliparity						
No vs. yes	0.802	0.392	**0.041**	2.230	1.034	4.809

p values < 0.05 are in bold

CI confidence interval, B is the estimated regression coefficient, and SE is the standard error of the coefficient

2.2-fold increases in the risk of endometriosis were observed with infertility ($p = 0.042$) and nulliparity ($p = 0.041$), respectively. Myoma size influenced the risk of endometriosis by a factor of 0.8 per cm ($p = 0.037$).

Discussion

In this cohort of patients receiving uterus-preserving laparoscopic myomectomy for symptomatic myomas, newly diagnosed endometriosis was found in 24.7%. Endometriosis was diagnosed in the peritoneum of the lesser pelvis (75.4%),

ovaries (12.3%), uterus (8.8%) and sacrouterine ligament (26.3%). The most common stages of endometriosis were rASRM I (29.8%) and II (29.8%). Severe endometriosis (rASRM III and IV) was rarely reported (12.3% and 10.4%).

Uterine leiomyomas and endometriosis are both oestrogen dependent. The range of similar potential symptoms, which correlated poorly with operative findings, makes surgical preoperative planning difficult. If endometriotic lesions are disregarded in the surgical therapy of uterine myomas, treatment of pelvic pain is likely to be inadequate. The aim of this study was to investigate the prevalence of unexpected coexistent endometriosis.

Previous studies confirmed a range of prevalence of 21–86% for the coexistence of endometriosis in surgical treatment of symptomatic myomas [14, 15]. Variations in study design, criteria for type of surgical intervention and patient population may contribute the discrepancy. Some studies included not only myomectomy but also hysterectomy [15]. Only women with completed family planning undergo a hysterectomy. Furthermore, the laparoscopic route allows an easier visualisation of endometriosis using a six to tenfold magnification and systems with high- or ultra-high-definition such as 4 K Ultra High Definition (UHD). As a routine in this study, the pelvis and the abdominal cavity in each case were carefully and systematically examined before starting the laparoscopic myomectomy procedure.

Myomas and endometriosis share potential causes, such as abnormal expression of aromatase with consequently hyperoestrogenic milieu [16]. Reported risk factors for the coexistence of uterine leiomyomas and endometriosis were younger age, nulliparity, polymenorrhea, smaller myomas and myoma location [17, 18]. Our study revealed no differences between the two groups in age of menarche and length of menstrual cycle, but a higher rate of nulliparity in women with endometriosis (66.7%) than in women without endometriosis (51.2%; $p = 0.04$). Our findings that age and BMI did not affect prevalence of endometriosis were consistent with other studies [14]. Patients without endometriosis smoked more cigarettes per day ($p = 0.04$). Only a smaller myoma size showed a significant influence on coexistent endometriosis (mean diameter 4.92 cm vs. 6.02 cm; $p = 0.006$). Number of myomas, weight and location had no influence on the rate of newly diagnosed endometrioses. Our findings were consistent with Isono et al. and other study groups [17, 18].

We found that initial symptoms influenced the prevalence of simultaneous endometriosis. Patients with infertility had a higher rate of coexistent endometriosis (31.6%) than patients without endometriosis (15.7%; $p = 0.01$). It is known that women with infertility have a higher prevalence of endometriosis. Endometriosis can result in a distortion of pelvic anatomy, such as tubal mobility reduction [19]. Symptoms such as bleeding disorders, pelvic pain and dysmenorrhea showed no differences. Previous studies found an influence of infertility and pain on the existence of endometriosis [14], but there was no differentiation in pelvic pain and dysmenorrhea.

The operative time was prolonged in cases with additional procedures for excision of endometriosis (168.47 min vs. 142.80 min; $p = 0.05$). 17.6% of coexistent endometrioses showed deep infiltrating lesions, most commonly of the sacrouterine ligament. Surgical procedures such as ureterolysis were necessary. These laparoscopic steps were time consuming and mainly responsible for higher grade complications, such as ureteral injuries [20]. Although additional surgical procedures were necessary to treat endometriosis, this did not seem to affect perioperative complications and length of hospital stay. This study had the advantage that all laparoscopic procedures were performed by surgeons with extensive experience in multivisceral endometriosis surgery.

The main findings of our study have important implications for preoperative examination, counselling and written consent. Uterine leiomyomas and endometriosis are the most common gynaecological diseases and have similar symptoms. The coexistence of endometriosis in patients with symptomatic uterine myomas should be considered, especially in women with infertility or nulliparity and women with smaller myomas. It can also assist in preoperative planning. Furthermore, if endometriotic lesions have been overlooked in the surgical therapy of uterine myomas, treatment of pelvic pain may be inadequate, patients may be unsatisfied and repeated surgeries may be necessary.

Conclusions

In conclusion, unexpected coexistent endometriosis in women who undergo laparoscopic myomectomy due to symptomatic uterine myomas should commonly be expected. Independent risk factors for this concomitant diagnosis were nulliparity, infertility and minor myoma size. The surgical treatment of coexistent endometriosis affected operative time, but not perioperative complications or length of hospital stay.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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