

Strong Association Between Endometriosis and Symptomatic Leiomyomas

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ABSTRACT

Background and Objectives: The relationship between leiomyoma and endometriosis is poorly understood. Both contribute to considerable pain and may cause subfertility or infertility in women. We conducted this retrospective study to assess the rate of coexistence of endometriosis in women with symptomatic leiomyoma. The primary outcome measured was the coexistence of histology-proven endometriosis in women with symptomatic leiomyoma.

Methods: This is a retrospective review of a data-based collection of medical records of 244 patients treated at a tertiary medical center, who were evaluated for symptomatic leiomyoma from March 2011 through December 2015. Of those, 208 patients underwent laparoscopic or laparoscopic-assisted myomectomy or hysterectomy. All patients provided consent for possible concomitant diagnosis and treatment of endometriosis. The remaining 36 patients underwent medical therapy and were excluded from the study. All patients who had myomectomy or supracervical hysterectomy underwent minilaparotomy for extracorporeal morcellation and specimen removal beginning in April 2012.

Results: Of the 208 patients with the presenting chief concern of symptomatic leiomyoma and who underwent surgical therapy, 181 had concomitant diagnoses of leiomyoma and endometriosis, whereas 27 had leiomyoma. Of the 27 patients, 9 also had adenomyosis. Patients with only fibroid tumors were, on average, 4.0 years older than those with endometriosis and fibroids (mean age, 44 vs 40 ± SD). Patients with both pathologies were also more

likely to present with pelvic pain and nulliparity than those with fibroid tumors alone.

Conclusions: In our patient population, 87.1% of patients with a chief concern of symptomatic fibroids also had a diagnosis of histology-proven endometriosis, which affirms the need for concomitant diagnosis and intraoperative treatment of both conditions. Overlooking the coexistence of endometriosis in women with symptomatic leiomyoma may lead to suboptimal treatment of fertility and persistent pelvic pain. It is important for physicians to be aware of the possibility of this association and to thoroughly evaluate the abdomen and pelvis for endometriosis at the time of myomectomy or hysterectomy in an effort to avoid the need for reoperation.

Key Words: Adenomyosis, Laparoscopy-assisted myomectomy, Minimally invasive surgery, Morcellation, Robotic surgery.

INTRODUCTION

Uterine leiomyoma is a benign transformation and proliferation of a single smooth muscle cell. It is the most common solid pelvic tumor, affecting 20–25% of reproductive-aged women, of whom 50% are symptomatic.^{1–5} The severity of symptoms associated with uterine leiomyoma depends on the number, size, and location of the tumor. The most common symptoms leading to treatment are abnormal uterine bleeding, pelvic pain and pressure.^{2,3,6} The growth and development of a myoma is multifactorial. Risk factors include increased estrogen stimulation including controlled ovarian stimulation, family history of uterine fibroid tumor, and race.¹ Growth hormone and human placental lactogen have also been shown to be major growth regulators of myomas.^{7,8}

Leiomyoma is seldom the sole cause of infertility, but data from several studies have demonstrated a link between fibroid tumors, fetal growth restriction, and premature delivery. Symptomatic leiomyoma is also a significant cause of hospitalization, high annual health costs, absence from work, and morbidity in women aged 15–54 years.^{4,5} Approximately 5–10% of patients with infertility have uter-

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ine fibroid tumors⁹ and are not a candidate for hormonal therapy, leaving myomectomy as the main option.

Endometriosis is also a common gynecologic condition, affecting 10–50% of reproductive-aged women.^{10,11} The most common symptoms are dysmenorrhea, chronic pelvic pain, dyspareunia, and subfertility. Its prevalence can be as high as 40% in infertile women^{12–15} and up to 87% in women with chronic pelvic pain.^{16,17} There has also been concern regarding the association between endometriosis and malignancy—specifically ovarian cancer.^{18–22} Patients with endometriosis also face the burden of high health costs before and after proper diagnosis.²³

The coexistence rate of endometriosis and leiomyoma continues to be poorly understood, as few studies have investigated the association.^{24–30} Dismissing the diagnosis of endometriosis during surgical intervention for fibroid tumors, can result in suboptimal treatment, especially in patients with chronic pelvic pain, infertility, or both. The purpose of our study was to investigate the incidence of coexisting endometriosis in patients undergoing surgical treatment for symptomatic uterine fibroid tumors without a known history of endometriosis.

METHODS

This study was a retrospective analysis of data collected from all patients who presented to the Center for Special Minimally Invasive and Robotic Surgery (Palo Alto, California, USA), a tertiary referral center for endometriosis, uterine fibroid tumors, infertility, and pelvic pain. Patients who were referred to the center for the specific treatment of leiomyoma from March 2011 through December 2015 with complaints of symptomatic uterine fibroids without a previous diagnosis of endometriosis were included in the

study. Patients who had a prior diagnosis of endometriosis were excluded. A total of 244 women with a chief concern of symptomatic leiomyoma with abnormal uterine bleeding without a prior diagnosis of endometriosis met inclusion criteria. Patients with fibroid tumors who also had a diagnosis of infertility and pelvic pain were included if they also had concomitant abnormal uterine bleeding.

At our institution, endometrial biopsy, magnetic resonance imaging, and lactate dehydrogenase levels are routinely performed on all patients with symptomatic fibroid tumors before undergoing surgery because of the recent controversy over leiomyosarcoma.³¹ Patients reporting menorrhagia or irregular bleeding underwent preoperative endometrial biopsy or diagnostic/operative hysteroscopy before myomectomy. All patients with a complaint of infertility had chromopertubation performed at the time of surgery. Tissue extraction was accomplished through extracorporeal morcellation, vaginally or via minilaparotomy.³²

Because information was obtained from the records in such a manner that human subjects could not be identified directly or through the identifier linked to the subjects, institutional review board approval was not necessary and a deidentifiable database was maintained.

Of the 244 patients who met the criteria, 36 elected not to undergo surgery and were excluded from the review. The remaining 208 patients underwent laparoscopic myomectomy (with or without robot assistance), laparoscopic-assisted myomectomy, or laparoscopic hysterectomy. In all patients, the indication for surgery was bleeding, infertility, and pain. Demographic data such as age, parity, and fertility history were collected from patients' medical records (**Tables 1** and **2**). Patients who were scheduled for myomectomy/hysterectomy were also asked to consent to

Table 1.

Characteristics of Patients With Uterine Fibroids and Associated Coexisting Extruterine Endometriosis vs Adenomyosis Alone

Patient Characteristics	Endometriosis and Fibroids (n = 181)	Fibroids Alone (n = 27)	P
Mean age, \pm SD ^a	40.7 \pm 6.20	44.5 \pm 8.13	0.036
Nulliparous, % ^b	68.0	37.5	0.005
Abnormal uterine bleeding alone, % ^b	38.0	45.0	0.51
Abnormal uterine bleeding and pain, % ^b	71.7	37.5	0.001
Abnormal uterine bleeding and infertility, % ^b	18.8	0.0400	0.08
Abnormal uterine bleeding and GI symptoms, % ^b	26.0	16.6	0.45

^aStudent's *t*-test.

^bFisher's exact test.

Table 2.
Patient Characteristics Associated With Mild and Severe Endometriosis

Patient characteristics	Minimal/Mild Endometriosis (n = 88) (Stages 1 and 2)	Moderate/Severe Endometriosis (n = 93) (Stages 3 and 4)	P
Mean age, \pm SD ^a	41.7 \pm 5.80	42.5 \pm 7.50	0.434
Nulliparous, % ^b	35.0	39.0	0.24
Abnormal uterine bleeding alone, % ^b	48.0	31.0	0.27
Abnormal uterine Bleeding and pain, % ^b	78.0	66.0	0.12
Abnormal uterine bleeding and infertility, % ^b	22.0	15.0	0.24
Largest fibroid <4 cm, % ^b	9.50	30.0	0.0009

^aStudent's *t*-test.

^bFisher's exact test.

treatment of endometriosis in the event of intraoperative diagnosis.

The advancement of the improved endoscopic camera and monitor technology allows for more detailed visualization of endometriotic lesions. Lesions that raise concern for endometriosis seen on laparoscopic survey were removed and confirmed by histologic examination of targeted biopsies. The revised American Society of Reproductive Medicine classification of endometriosis was used to assess for severity of disease,³³ which was classified as minimal (stage 1), mild (stage 2), or moderate (stage 3) to severe (stage 4).

Statistical analyses were performed with SPSS for Windows (SPSS, Inc., Chicago, Illinois, USA). Student's *t* test was used to compare normally distributed data. Fisher's exact test was used to compare categorical data. All reported *P*-values are 2 sided, so both directions of alpha were tested for statistical significance; *P* < .05 was statistically significant.

RESULTS

A total of 208 patients underwent surgical treatment for symptomatic uterine fibroid tumors during the study period. Most patients underwent laparoscopic or laparoscopic-assisted myomectomy (71.6%) compared with hysterectomy (28.3%). Five cases were performed with assistance of the robotic platform. The chief concern of all patients was abnormal uterine bleeding, with 84% of the study population also reporting pelvic pain; 20.7% reporting infertility; 20.7% reporting dyspareunia; 21.2% reporting urinary symptoms including frequency, urgency, and dysuria; and 21.2% reporting gastrointestinal symptoms,

including dyschezia and alternating constipation and diarrhea during menses.

Histology-proven leiomyoma were found in all patients. Of the subjects, 181 (87.1%) had endometriosis noted at the time of surgery and subsequently confirmed by histology. Of the 27 patients where endometriosis was not noted at the time of laparoscopic survey, 9 had adenomyosis on the final histology report. Only 18 patients (8.6%) were diagnosed solely with uterine fibroids after surgical evaluation. A total of 124 patients had a large fibroid tumor weighing more than 100 g, and of those, 107 (86.2%) had associated endometriosis on the pathology report. The average weight of the fibroids was 381 g, with the weights ranging from 19.9 to 3000 g. This average and range are based on 160 patients' pathologies, as 48 pathology reports did not include the weights of the tumor. Concomitant diagnosis of endometriosis was noted in 181 of the 208 (87%) patients and 93 of those (51.3%) had moderate to severe disease (stage 3 and 4). Of the patients who reported dyspareunia, urinary symptoms, and gastrointestinal symptoms, 81%, 69%, and 91.8% respectively, had concomitant histologic diagnosis of endometriosis.

Patients who had concomitant leiomyoma and endometriosis were on average 4.0 years younger than patients with leiomyoma alone (40.7 vs 44.5; *P* = .036; **Table 1**). Patients between the ages of 30 and 39 had a 56% prevalence of endometriosis, occurring in 40% of those 40–49 years of age and in only 0.038% of women aged 50 and older. In our cohort, we had 3 patients above 60 years of age, and none of them had endometriosis at the time of surgery or on their final pathology specimens.

Of the patients with a concomitant diagnosis of both fibroid tumor and endometriosis, 71.7% had more pronounced pelvic pain when compared with the fibroid-only group ($P = .001$). Nulliparous patients were also more likely to be simultaneously diagnosed with both endometriosis and fibroid tumor than with fibroid tumor alone ($P = .005$). Similarly, infertile women were more likely to have both diagnoses ($P = .08$), although these differences did not reach significance.

We compared patients with mild (stage 1 and 2) endometriosis with those with severe (stage 3 and 4) endometriosis. Patients with smaller fibroid tumors, (<4 cm or <100 g in weight), were significantly more likely to have severe endometriosis than those with larger fibroid tumors ($P = .0009$; **Table 2**). There was no significant difference in abnormal uterine bleeding, pain, nulliparity, and infertility between the 2 groups.

From our cohort of 208 women, 202 were discharged home on the same day as their surgery. There were 3 total intra- and postoperative complications. The first was an incidental cystotomy repaired laparoscopically during total laparoscopic hysterectomy in a patient with stage 4 endometriosis, extensive adhesions, and a fibroid uterus weighing 606 g on final pathology report. She had an uneventful recovery without any sequelae. The second patient had a vaginal cuff hematoma after total laparoscopic hysterectomy for stage 4 endometriosis, extensive adhesions, and a 122-g fibroid uterus. An incision and drainage of the vaginal cuff was performed, and the patient recovered well. The last complication involved a patient who required a postoperative blood transfusion after laparoscopic-assisted myomectomy for a 3000-g fibroid uterus. No endometriosis was noted at the time of the laparoscopic survey, but the final pathology reported revealed adenomyosis.

DISCUSSION

Endometriosis and uterine fibroids are common disorders that affect a significant number of women. It is estimated that 25% of women over the age of 36 have 1 or more leiomyomas, with 50% of these being symptomatic.¹⁸ Our study shows that it is possible for women to have both of these conditions at the time of surgery, emphasizing the importance of keeping a broad differential both before and during surgery. Should endometriotic lesions be overlooked at the time of surgical treatment for fibroid tumors, treatment of pain may be suboptimal. Both conditions are estrogen-dependent, which is congruent with our observation that endometriosis had increased prevalence in a

younger patient population. This finding is consistent with previous studies associating younger age, higher estrogen levels, and increased prevalence of disease during reproductive years^{34,35} and improvement after menopause.³⁶

The goal of our study was to assess the prevalence of endometriosis in our patient population with symptomatic leiomyoma as defined by abnormal uterine bleeding. Strengths of the study include a single senior surgeon with decades of experience performing all surgeries, which decreased the inconsistency in diagnosis of endometriosis between surgeons at the time of laparoscopy. In addition to its retrospective design, a limitation to our study is that we are a tertiary referral center specializing in the treatment of endometriosis which introduces a potential population bias. We would expect the incidence of endometriosis in our patient population to be higher than that of the general population. However, given that we found that most of our patients had concomitant endometriosis at the time of surgery for treatment of uterine fibroid tumor, we believe that this association deserves further investigation.

The current literature reports an incidence of concomitant fibroids and endometriosis ranging between 12 and 20%, based on 2 previously published studies.^{23,24} The first was a large multicenter study conducted in Italy involving more than 3600 patients, 735 of whom had an indication for surgery that did not include fibroid tumor or pain.²⁴ The second study was performed in Finland and included 605 participants, 183 of whom underwent tubal ligation for sterilization. Our study limited inclusion of patients to those with fibroid tumor and complaints of abnormal uterine bleeding. Tanmahasamut et al²⁹ diagnosed endometriosis by pathology report or visual inspection, not necessarily both. Thus, it is possible that endometriotic lesions were miscategorized or missed altogether at the time of surgery. Our study required the diagnosis of endometriosis to be made by both laparoscopic survey and pathologic confirmation, and our observed incidence of coexisting fibroid tumor and endometriosis was significantly higher than that reported in the current literature.

Based on these preliminary findings, we believe that in a subset of patients with symptomatic fibroid tumors and pelvic pain, endometriosis must be seriously considered as a concomitant diagnosis and may be more common than previously thought. Because of the multifaceted nature of this disease, endometriosis is often called the great masquerader³⁷ or the chameleon of the pelvis,³⁸ as lesions are easily overlooked. It is especially possible to miss it by laparotomy, because one may not be able to completely

visualize the posterior cul-de-sac, ovarian fossa, and broad ligaments in great detail. It is well recognized that optimal visualization provided by laparoscopy enhances diagnosis of the disease.³⁴ In our study, thorough and systematic visual inspection was performed, and all possible lesions were biopsied, with histology-proven disease described in the cohort. It is possible that our higher incidence of coexisting disease found at the time of fibroid treatment was due to our high index of suspicion for endometriosis, which led to a careful and methodical survey of the abdomen and pelvis.

There was no significant difference in the prevalence of minimal/mild and moderate/severe endometriosis in our cohort of patients with symptomatic fibroid tumors. Although one might expect stage 1 and 2 disease to be more common in all women, including women with fibroid tumors, it is possible that these patients first explored medical therapy, which would delay their diagnosis and allow progression of the endometriosis. In addition, specifically for the subset of patients with fibroid tumors undergoing infertility treatment, controlled ovarian stimulation can worsen endometriosis as well.

All except 1 of our patients with infertility and symptomatic fibroid tumors were found to have endometriosis as well. In addition, nulliparous patients were more likely to be simultaneously diagnosed with the 2 pathologies, which is consistent with the current literature, as the relationship between endometriosis and subfertility has been well documented.^{39,40} There is a reduced monthly fecundity rate (2–10%) in patients with endometriosis, as compared with fertile couples (15–20%).⁴¹ There is also an increased monthly fecundity rate and cumulative pregnancy rate after surgical removal of stage 1 and 2 endometriosis.^{34,42}

We were surprised to find that in our study population, women with smaller fibroid tumors had more severe (stage 3 and 4) endometriosis. Physiologically, we expected the opposite, because both disease processes are hormonally driven. One potential explanation is that women who have only fibroid tumors may be able to avoid surgical intervention until the tumor reaches a critical mass where the bleeding and pressure symptoms become unbearable. However, women who have severe endometriosis may have severe pain in addition to bothersome abnormal uterine bleeding that leads them to undergo surgery sooner as compared to their fibroid-only counterparts. Future studies should be performed to investigate this further.

Based on the prevalence of myomas (1:5), roughly more than 700 million women will have a fibroid tumor during their reproductive years. Our preliminary results suggest that the incidence of endometriosis in these women is higher than currently reported in the literature. Presently, there is a paucity of information describing the coexistence between the 2 pathologies. Prospective studies evaluating for endometriosis at the time of surgery for uterine fibroids are currently lacking and constitute an area for further future investigation.

CONCLUSION

Our findings demonstrate that patients who have symptomatic leiomyoma may be at higher risk for endometriosis as well. Because of the significant overlap of symptoms, it is often difficult to discern which pathology is responsible for the patient's complaints. This highlights the importance of maintaining a high level of suspicion for endometriosis before and during surgery in these women, with the goal of treating both pathologies in a single surgery. One should be especially mindful of young patients who present with uterine fibroid tumors, abnormal uterine bleeding, and subfertility or nulliparity and those who present with pain disproportionate to the size of the tumor. Failure to diagnose and treat can lead to continued pain, subfertility, and need for reoperation. Additional investigation is needed to further validate and quantify our observation.

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