

Coexistence of endometriosis in women with symptomatic leiomyomas

Jian Qun Huang, M.D.,^a Ruth Bunker Lathi, M.D.,^a Madeleine Lemyre, M.D.,^a
Hilda Elena Rodriguez, M.D.,^a Ceana H. Nezhat, M.D.,^b and Camran Nezhat, M.D.^a

^a Stanford University Medical Center, Department of Obstetrics and Gynecology, Palo Alto, California; and ^b Center for Special Minimally Invasive Surgery and Reproductive Medicine, Northside Hospital, Atlanta, Georgia

Objective: To investigate the coexistence of endometriosis in women presenting with symptomatic leiomyomas.

Design: Retrospective study.

Setting: Tertiary university medical center.

Patient(s): We reviewed the medical records of 131 patients who underwent laparoscopic myomectomy or hysterectomy. All patients were consented for possible concomitant diagnosis and treatment of endometriosis.

Intervention(s): All patients underwent laparoscopic myomectomy or hysterectomy.

Main Outcome Measure(s): The main outcome measure of the study was the presence or absence of endometriosis.

Result(s): Of the 131 patients, 113 were diagnosed with endometriosis and fibroids, while 18 were diagnosed with fibroids alone. Patients with fibroids were on average 4.0 years older than those with endometriosis and fibroids (41 vs. 45). Patients with both diagnoses were also more likely to present with pelvic pain and nulliparity than those with fibroids alone.

Conclusion(s): An overwhelming majority of patients with symptomatic fibroids were also diagnosed with endometriosis. Overlooking the concomitant diagnosis of endometriosis in these women may lead to suboptimal treatment of the patients. Further studies are needed to evaluate the impact of surgical treatments on symptom resolution. (*Fertil Steril*® 2010;94:720–3. ©2010 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, leiomyomas, laparoscopic treatment

Uterine leiomyoma or fibroid tumors are benign monoclonal tumors arising from the smooth muscle cells of the myometrium. By age 50, their estimated cumulative incidence is >80% for black women and nearly 70% for white women (1). Their pathogenesis is still unclear and likely involves genetic predisposition, steroid hormones, and growth factors (2). While many patients are asymptomatic, fibroids can result in abnormal uterine bleeding, pelvic pain and pressure, or reproductive dysfunction. Leiomyoma is still the most common indication for hysterectomy in the United Kingdom and United States (3). Leiomyomas are present in approximately 5%–10% of infertility cases (4), and pregnant women with leiomyomas face a 10% rate of obstetrical complications (5). Myomectomy can improve fertility and pregnancy outcomes in some subgroups of infertile patients (6).

Pelvic endometriosis is another common gynecologic condition that affects young women. It was first recognized in the early 1900s (7–9) and is estimated to affect 2%–10% of reproductive-age women (10, 11). In women with pelvic pain, infertility, or both, the frequency of endometriosis approaches 35%–50% (12–14). It is also well recognized that the risk of endometriosis is higher in young women with primary amenorrhea and outlet obstruction to menstrual flow. This is postulated to be due to the higher volume of refluxed menstrual blood and endometrial tissue fragments (15), in accordance with the theory that endometriosis is the result of retrograde menstruation.

In a recent large epidemiological study involving 2777 subjects, leiomyomas were noted to be a significant risk factor for the presence of endometriosis (16). Additionally, biochemical and molecular studies have shown that intrinsic molecular aberrations in 17 β -hydroxysteroid dehydrogenase and aromatase expression may contribute to the development of both leiomyomas and endometriosis (17). Because uterine fibroids are commonly seen on ultrasound, they are frequently the indication for surgical intervention. However, the rate of coexistence of uterine fibroids and endometriosis is poorly understood and if overlooked may lead to

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Reprint requests: Dr. Camran Nezhat, Stanford University Medical Center, Center for Special Minimally Invasive Surgery, 900 Welch Road, Suite 403, Palo Alto, California 94304 (FAX: 650-327-2794; E-mail: cnezhat@stanford.edu).

suboptimal treatment of a patient's symptoms. If patients undergo treatment of uterine fibroids by hysteroscopy or laparotomy alone, endometriosis will not be reliably diagnosed.

We conducted a retrospective study to evaluate the prevalence of endometriosis in women undergoing laparoscopic treatment for symptomatic leiomyomas either by myomectomy or hysterectomy. The goal of the study was to ascertain the rate of coexistence of the two conditions and to identify the characteristics of the patient population at increased risk for concomitant diagnoses.

MATERIALS AND METHODS

The study protocol was reviewed and approved by the Institutional Review Board of Stanford University Medical Center. Between September 2002 and January 2006, 131 women without a prior history of endometriosis presented to our tertiary center with symptomatic leiomyomas requiring surgical intervention. The presence of leiomyomas was confirmed by a pelvic exam or ultrasound. The patients were included in the study only if endometriosis had not been diagnosed previously.

Baseline characteristics such as age, parity, surgical and fertility history, presenting symptoms, and preoperative fibroid size were collected from patient charts. Patients who were scheduled for laparoscopic myomectomy/hysterectomy also consented for treatment of endometriosis if it was diagnosed intraoperatively. Endometriosis was diagnosed by visualization of clinically evident lesions and/or pathologic confirmation of targeted biopsies. The revised American Society of Reproductive Medicine classification of endometriosis was used to assess the stage of the condition (18). Operative and pathology reports were reviewed on all the patients to confirm the presence and size of leiomyomas as well as the presence and extent of endometriosis. Endometriosis was classified as absent, mild (American Fertility Society [AFS] stage 1 or 2), or severe (AFS stage 3 or 4) by visual inspection and biopsy results when applicable. All laparoscopic procedures were performed by the senior author (CN).

Statistical analyses were performed using SPSS for Windows (SPSS, Inc., Chicago). 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 two sided, and *P* < .05 was considered statistically significant.

RESULTS

The most commonly reported symptom was pelvic pain and/or pressure (84%), followed by menorrhagia (46%) and infertility (18%). Most patients underwent laparoscopic myomectomy (78%) compared with hysterectomy (22%). Pathology-proven leiomyomas were found in all patients. Concomitant diagnosis of endometriosis was noted in 86% of patients, of which 20% had severe disease. Of the 18 patients who were not diagnosed with endometriosis, six of them were found to have adenomyosis based on the pathology report. Only 12 of the 131 patients in our study

had the diagnosis of fibroids alone after undergoing laparoscopy. Our data seem to suggest that our patients' symptoms may be due to their concomitant diagnoses, endometriosis and adenomyosis, rather than to the fibroids alone.

We compared the patients with concomitant fibroids and endometriosis to those with fibroids only. The results are presented in Table 1. Patients with fibroids alone were on average 4.0 years older than those with endometriosis and fibroids (41 vs. 45; *P* = .007). This is consistent with previous studies suggesting that the risk of endometriosis increases after menarche and then falls as the menopause approaches (19). When compared with patients who underwent the procedure at age 40 or older, the patients at age 30–39 years were more likely to be diagnosed with endometriosis (92% vs. 83%). The incidence of endometriosis was lowest in women 50 years or older.

Patients with fibroids who complained of pelvic pain were more likely to be diagnosed with endometriosis intraoperatively than were patients with fibroids who did not have a complaint of pain (*P* = .0006). Nulliparous and infertile patients were also more likely to be diagnosed with endometriosis and fibroids rather than with fibroids alone (*P* = .05 and *P* = .07, respectively). In contrast, the percentage of patients who presented with menorrhagia, pelvic pressure, and large fibroids was not found to be significantly different between the two groups.

We then performed a similar analysis comparing patients diagnosed with mild endometriosis with those with severe endometriosis. The results are presented in Table 2. We found that patients with smaller dominant fibroids are significantly more likely to have severe endometriosis than those with fibroids 4 cm or larger (*P* = .02). The percentages of patients presenting with pain, nulliparity, infertility, pelvic pressure, and menorrhagia were not found to be different in the two groups.

DISCUSSION

Uterine leiomyomas and endometriosis have many common features. Both are hormone-dependent conditions that can often be the source of pelvic pain and menstrual abnormalities. In addition, both have a range of symptom severity that is often poorly correlated to preoperative or operative findings, making surgical planning a challenge. The goal of our study was to investigate the prevalence of coexistence of the two complex diseases. In our search of the literature, we only found one multi-center study, conducted in Italy, investigating the prevalence of endometriosis in patients with fibroids. The investigators reported a 12% coexistence of the two conditions. The majority of the patients were diagnosed with third- and fourth-stage endometriosis (20).

In contrast to the Italian study, we found that 86% of the patients who presented for surgical treatment of symptomatic fibroids had a concomitant diagnosis of endometriosis. The vast majority of our patients were diagnosed with stage

TABLE 1**Patients with fibroids and endometriosis versus fibroids alone.**

Patient characteristics	Endometriosis and fibroids (n = 113)	Fibroids alone (n = 18)	P value
Mean age, \pm SD ^a	41 \pm 5.7	45 \pm 5.9	.007
Parous, % ^b	30	55	.05
Menorrhagia, % ^b	46	66	.13
Pain, % ^b	61	16	.0006
Pressure, % ^b	38	27	.43
Infertility, % ^b	18	0	.07
Largest fibroid <4 cm, % ^b	35	22	.41

^a Student's *t*-test.^b Fisher's exact test.Huang. Coexistence of endometriosis and leiomyomas. *Fertil Steril* 2010.

I-II endometriosis and reported pelvic pain and menorrhagia as their primary complaints. The discrepancies between the two studies may be partially due to the fact that our practice has a great interest in endometriosis and functions as a referral base for difficult gynecologic cases. In addition, all of our patients underwent laparoscopy under the guidance of a practitioner with extensive experience in recognizing and diagnosing endometriosis, whereas the patients in the Italian study underwent a mixture of laparotomy and laparoscopy. As documented previously in the literature, with the improved visualization, laparoscopy provides an easier diagnosis and biopsy of mild endometriosis than laparotomy (19).

In our study, a careful and systematic inspection of the pelvic and abdominal cavity was carried out for every patient. All lesions suspicious for endometriosis that were biopsied had histopathologic confirmation of the disease.

Of the 14 patients in our study who had previously undergone exploratory laparotomy or abdominal myomectomy, all but one patient were subsequently diagnosed with endometriosis. This underscores the fact that exploratory laparotomy

can often underestimate the prevalence of endometriosis. Nine patients had prior laparoscopic procedures for various gynecologic conditions and were not given a diagnosis of endometriosis. Eight of them were subsequently found to have endometriosis during the study period. This discrepancy may be related to the fact that an average of 9.7 years had passed since their preceding surgeries and endometriosis may have developed *de novo* in the elapsed interval.

An overwhelming majority of the patients with symptomatic fibroids who presented to our practice were diagnosed with endometriosis. Patients with the concomitant diagnoses of both conditions were younger, nulliparous, and presented with pelvic pain that was often disproportionate to the size of their fibroids. Size of the dominant fibroid was the only factor that showed an inverse association with the severity of endometriosis.

Interestingly, all patients with infertility in our study were diagnosed with endometriosis. It is well-known that infertile women have a significantly higher prevalence of endometriosis and are significantly more likely to have moderate to severe endometriosis than fertile women (21). Advanced endometriosis can often result in distortion of the pelvic

TABLE 2**Patients with mild endometriosis versus severe endometriosis.**

Patient characteristics	Mild endometriosis (n = 90)	Severe endometriosis (n = 23)	P value
Mean age, \pm SD ^a	41.6 \pm 5.3	40.5 \pm 7.3	.43
Parous, % ^b	32	26	.45
Menorrhagia, % ^b	47	39	.81
Pain, % ^b	60	65	.81
Pressure, % ^b	41	30	.47
Infertility, % ^b	16	26	.36
Pressure, % ^b	41	30	.47
Largest fibroid <4 cm, % ^b	29	56	.02

^a Student's *t*-test.^b Fisher's exact test.Huang. Coexistence of endometriosis and leiomyomas. *Fertil Steril* 2010.

anatomy such as tubal obstruction or limited tubal mobility and can reduce the efficacy of fimbrial pickup of the ovum, all of which can lead to subfertility. Expectant management of endometriosis has been reported to have monthly fecundity rates of 8.7%, 3.2%, and 0% and pregnancy rates of 33%, 25%, and 0% in patients with mild, moderate, and severe endometriosis, respectively (22).

Laparoscopic treatment for endometriosis has been shown to increase fecundity. In 1997, Marcoux et al. randomized infertile women affected by endometriosis to operative or diagnostic laparoscopy. These women were then followed for 36 weeks after the procedure, and pregnancy outcome was reported. Laparoscopic surgery increased the cumulative probability of a pregnancy that lasted more than 20 weeks by 73%. The fecundity rates were 4.7 versus 2.4 per 100 person-months. The absolute increase in the 36-week probability of a pregnancy carried beyond 20 weeks attributable to laparoscopic surgery was 13% (23). Littman et al. conducted a retrospective case series examining the effect of laparoscopic treatment of endometriosis on patients with multiple IVF failures. The study showed that of the 29 patients with prior IVF failures, 22 conceived after laparoscopic treatment of endometriosis, of which 15 were non-IVF pregnancies. The investigators concluded that in patients with failed IVF, laparoscopic evaluation and treatments by a skilled surgeon should be considered before egg donation or adoption (24).

In light of the findings of our study, it is advisable to counsel patients with symptomatic leiomyomas of the high likelihood that a concurrent diagnosis of endometriosis may be made and to strongly consider surgical evaluation and treatment for both disorders. Endometriosis and leiomyomas can often have significantly negative effects on multiple facets of a woman's life. Due to the significant overlap of the symptoms that are shared by the two conditions, it is often difficult to discern which pathology is responsible for various symptoms. Therefore we must adopt a thorough and systematic approach in all patients with symptomatic fibroids undergoing laparoscopy to ensure adequate inspection for treatment and diagnosis of endometriosis. We should be especially mindful of young patients with subfertility or nulliparity and those who present with pain disproportionate to the size of their fibroids.

Failure to diagnose and treat both etiologies of the patient's symptoms may lead to higher treatment failure rates as well as an increased recurrence rate.

REFERENCES

- Day Baird D, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol* 2003;188:100-7.
- Stewart EA. Uterine fibroids. *Lancet* 2001;357:293-8.
- Manyonda I, Sinthamoney E, Belli AM. Controversies and challenges in the modern management of uterine fibroids. *Br J Obstet Gynecol* 2004;111:95-102.
- Rackow BW, Arici A. Fibroids and in-vitro fertilization: which comes first? *Curr Opin Obstet Gynecol* 2005;17:225-31.
- Katz VL, Dotters DJ, Droegemeuller W. Complications of uterine leiomyomas in pregnancy. *Obstet Gynecol* 1989;73:593-6.
- Bulletti C, De Ziegler D, Polli V, Flamigni C. The role of leiomyomas in infertility. *J Am Assoc Gynecol Laparosc* 1999;6:441-5.
- Sampson JA. Perforating hemorrhagic cysts of the ovary: their importance and especially their relation to pelvic adenomas of endometrial type. *Arch Surg* 1921;3:245-323.
- Sampson JA. Ovarian hematomas of endometrial type (perforating hemorrhagic cysts of the ovary) and implantation adenomas of the endometrial type. *Boston Med Surg J* 1922;186:445-56.
- Shirer JW. Endometriosis: a pathological study of thirty cases. *Can Med Assoc J* 1928;18:151-5.
- Vessey MP, Villard-Mackintosh L, Painter R. Epidemiology of endometriosis in women attending family planning clinics. *Br Med J* 1993;306:182-4.
- Kjerfulff HK, Erickson BA, Langerberg PW. Chronic gynecologic conditions reported by US women: findings from National Health Information Survey, 1984-1992. *Am J Pub Health* 1996;86:195-9.
- Sangi-Haghpeykar H, Poindexter AN. Epidemiology of endometriosis among parous women. *Obstet Gynecol* 1995;85:983-92.
- Chatman DL, Ward AB. Endometriosis in adolescents. *J Reprod Med* 1982;27:156-60.
- Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. *Am J Epidemiol* 2004;160:784-96.
- Giudice LC, Kao LC. Endometriosis. *Lancet* 2004;364:1789-99.
- Hemmings R, Rivard M, Olive D, Poliquin-Fleury J, Gagne D, Hugo P, et al. Evaluation of risk factors associated with endometriosis. *Fertil Steril* 2004;81:1513-21.
- Bulun SE, Imir G, Utsunomiya H, Thung S, Gurates B, Tamura M, et al. Aromatase in endometriosis and uterine leiomyomata. *J Steroid Biochem Mol Biol* 2005;95:57-62.
- American Society for Reproductive Medicine. Revised American Society for American Society for Reproductive Medicine Classification of Endometriosis: 1996. *Fertil Steril* 1997;67:817-21.
- Houston DE. Evidence for the risk of pelvic endometriosis by age, race and socioeconomic status. *Epidemiol Rev* 1984;6:167-91.
- Gruppo Italiano per lo studio dell'endometriosi. Prevalence and anatomical distribution of endometriosis in women with selected gynecological conditions: results from a multicentric Italian Study. *Hum Reprod* 1994;9:1158-62.
- D'Hooghe TM, Debrock S, Hill JA, Meuleman C. Endometriosis and subfertility: is the relationship resolved? *Semin Reprod Med* 2003;1:243-253.
- Olive DL, Stohs GF, Metzger DA, Franklin RR. Expectant management and hydrotubations in the treatment of endometriosis-associated infertility. *Fertil Steril* 1985;44:35-42.
- Marcoux S, Maheux R, Berube S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. *New Engl J Med* 1997;337:217-22.
- Littman E, Giudice L, Lathi R, Berker B, Milki A, Nezhat C. Role of laparoscopic treatment of endometriosis in patients with failed in vitro fertilization cycles. *Fertil Steril* 2005;84:1574-7.