

Leiomyoma Recurrence after Uterine Artery Embolization

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PURPOSE: The purpose of this study was to evaluate the rate of leiomyoma recurrence after uterine artery embolization (UAE) for symptomatic uterine leiomyomas.

MATERIALS AND METHODS: A prospective study of UAE of uterine leiomyomas has been ongoing at the authors' hospital since 1997. The recurrence rate was assessed in June 2002. Vascular access was obtained via the right common femoral artery and free-flow embolization was performed with use of 150–250- μ m polyvinyl alcohol particles and an absorbable particle sponge. Follow-up included clinical and ultrasound (US) examinations at 3, 6, and 12 months, and once per year thereafter.

RESULTS: Eighty-five UAE procedures were performed between January 1997 and June 2000. Five patients were lost to follow-up. Median follow-up was 30 months (range, 2–57 months). There were six immediate failures: one technical failure, three cases of concomitant disease (one case of endometrial cancer and two cases of adenomyosis), and two cases of large subserosal leiomyomas. There were eight late failures or recurrences: one case of leiomyoma progression, seven cases of new leiomyomas. Mean time to recurrence was 27.4 months.

CONCLUSIONS: Although UAE is an effective primary treatment for leiomyomas, this study recorded a recurrence rate of 10% at just more than 2 years. Clinical and US examinations are needed before UAE to exclude pedunculated submucosal leiomyomas and cancers, and must be repeated for more than 2 years after UAE to monitor patients' progress. Longer follow-up and more events are needed to define risk factors for recurrence.

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Abbreviations: PVA = polyvinyl alcohol, UAE = uterine artery embolization

UTERINE artery embolization (UAE) is an effective new treatment for symptomatic uterine leiomyomas that successfully controls symptoms in 85%–95% of patients (1–3). Leiomyomas derive their blood supply almost exclusively from the uterine arteries;

occluding these arteries results in ischemia and leiomyoma shrinkage despite persistent myometrial vascularity (4). For instance, a decrease in leiomyoma volume from –29% at 3 months to –86% at 24 months has been reported (5).

Failures may be of two kinds. Immediate failures, which are well documented in the literature (6–15), cover technical failure (unsuccessful embolization), method failure because of persistence of symptoms for 6 months or longer (as often the case for large subserosal leiomyomas or submucosal leiomyomas), and failure caused by overlooking diseases such as cancer or adenomyosis. A case of undiagnosed leiomyosarcoma was reported recently (14). On the other hand, late failures involve failure of the technique because of progression of an ex-

isting leiomyoma or failure of the method because of the occurrence of new leiomyomas. A potential cause of recurrence could be, for example, a continued blood supply from the ovarian artery. However, very few cases of leiomyoma recurrence have yet been reported after UAE. This may be because follow-up in most studies does not exceed 12 months (16–20). The distinction between early and late failures is important as it might help elucidate the natural history of leiomyomas and help compare the true success rates of embolization techniques and alternative treatments.

In 1997, the authors initiated a prospective study of UAE of uterine leiomyomas. In this article, the rate of immediate failures and evaluate late failures is reported.

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Mean Volume of the Uterus and of Leiomyomas as Shown with Ultrasound Before and After UAE

	Before	2 Months	6 Months	12 Months	24 Months	36 Months	48 Months
Uterus (mm ³)	373,315 (52)	276,737 (41)	250,457 (35)	172,591 (31)	189,152 (26)	145,098 (20)	254,654 (5)
Leiomyoma (mm ³)	156,808 (75)	91,972 (65)	76,333 (50)	62,359 (46)	51,826 (37)	42,282 (22)	74,391 (7)

Note.—Patient numbers are shown in parentheses.

PATIENTS AND METHODS

Study Population

UAE was offered as an alternative to surgery to all women with one or more symptomatic uterine leiomyomas unless a concomitant condition (adnexal mass, uterine prolapse, stress incontinence) warranted surgery. The diagnosis was established by suprapubic and transvaginal ultrasound (US) and by power Doppler imaging of the genital tract. Menopausal women or women with metrorrhagia underwent preprocedure endometrial sampling.

Between January 1997 and June 2000, 85 UAE procedures were performed. The patients presented with abnormal bleeding ($n = 21$), bulk-related symptoms ($n = 13$), or both ($n = 51$). Before UAE, all patients signed an informed consent form according to local Ethics Committee requirements. The median patient age was 43.8 years (range, 31–65 years). The mean number of leiomyomas was 1.9 (range, 1–5). Location of the main leiomyoma was intramural in 61 women, subserosal in 13 women, and partly submucosal in six. A surveillance protocol, written at the start of the study, was used to study immediate failure rates and recurrence rates. Five patients were lost to follow-up; one patient moved to an unknown address and four patients were contacted but refused an appointment for an US examination. During this 3.5-year period, the team performed 228 abdominal hysterectomies, 206 vaginal hysterectomies, eight laparoscopic hysterectomies, 52 myomectomies, and 68 resections by hysteroscopy for symptomatic leiomyomas.

UAE Technique

Vascular access was via the right common femoral artery. Catheterization of the uterine arteries was

achieved with a single 4- or 5-F Cobra catheter (Terumo, Inc., Guyancourt, France). Free-flow embolization of the left and right uterine arteries was achieved with 150–250- μ m polyvinyl alcohol (PVA) particles. An absorbable particle sponge afforded more definitive proximal embolization and minimized the risk of particle reflux. The choice of particle size and protocol was based on the work of Ravina et al (1). The endpoint for embolization was stasis in the proximal uterine artery on angiographic imaging. Pre- and postembolization arteriography with iobitridol as contrast medium (Xenetix; Guerbet, Roissy, France) was used to establish successful bilateral uterine artery occlusion.

Study Endpoints

Follow-up after discharge from hospital included clinical and ultrasound examinations at 3, 6, 12 months and once per year after the first year. Throughout follow-up, each patient was always seen by the same practitioner who used a simple questionnaire designed to collect prospectively all the clinical and US data needed to establish relapse or recurrence. Clinical symptoms were classified as increased, unchanged, improved, or resolved. Uterus size and volume, and the size, volume, location, and vascularization of the largest fibroid were established by the same sonographic methods as used before UAE. Immediate failure was defined as unsuccessful embolization or no change in symptoms. In such cases, hysterectomy was proposed. Recurrence was defined both clinically (reappearance of symptoms) and anatomically (increase in leiomyoma size or detection of new leiomyomas).

RESULTS

Median and average follow-up was 30 months. After UAE, most patients (83.5%) experienced clinical improvement of symptoms. There were 14 failures resulting from either embolization failure or leiomyoma recurrence. All of these 14 patients were offered alternative treatment. Mean time to further treatment after failure was 12.3 months. Mean time to recurrence was 27.4 months. Uterus and leiomyoma volumes before UAE and at different times after UAE are shown in the Table.

Of the 14 failures, six were immediate failures: a case of dissection of the external iliac artery during catheterization (the patient refused a repeat UAE and underwent hysterectomy), two cases of adenomyosis (diagnosed by histologic examination of the hysterectomy specimens), two cases of large subserosal leiomyomas, and a case of endometrial cancer. This was a 37-year-old woman, G0 P0, with a BMI of 20 who presented with menometrorrhagia. A single 10-cm interstitial leiomyoma detected by US showed good imaging results after UAE but symptoms persisted. On hysteroscopy, endometrial cancer was found.

Eight late failures or recurrences were encountered; one case of leiomyoma progression and seven cases of new leiomyomas were revealed by symptom recurrence.

Leiomyoma Progression

A 41-year-old woman, G2 P0, experienced bulk-related symptoms. Physical examination revealed a “24-week” uterus with multiple fibroids. According to pelvic US, the uterus measured 131/80/77 mm and presented multiple vascular leiomyomas. The largest leiomyoma measured 33 mm. Although uterus size decreased to 106/68/59 mm (16-weeks) 12 months after

UAE, it increased to 126/84/83 mm at 2 years, and 160/100/86 mm at 3 years. The leiomyoma was reduced to 25 mm at 12 months but increased to 44 mm at 2 years and 67 mm at 3 years. According to Doppler imaging, the vessels of the leiomyoma disappeared after UAE but returned as leiomyoma size increased. Surprisingly, the patient experienced bulk-related symptoms only 3 years after UAE. The patient refused a repeat UAE procedure and a hysterectomy was performed. The pathology report confirmed the presence of multiple leiomyomas; the largest was 7 cm. Hyaline degeneration was present but neither complete necrosis nor infarction. A foreign body reaction was visible around many of the intramyoma vessels.

Occurrence of New Leiomyomas

Of the seven new leiomyomas, two were intramural and five were submucosal. The two intramural leiomyomas are described first.

A 36-year-old, nulliparous, woman had a history of bulk-related symptoms. Physical examination revealed a "20-week" uterus with multiple fibroids. Pelvic US revealed two fibroids (95 mm and 65 mm in diameter, respectively) and UAE was performed. There were no immediate complications and pain lasting 3 weeks was controlled by oral medication. Pelvic US at 3 months after UAE showed two avascular leiomyomas measuring 78 mm and 58 mm in diameter, respectively. Bulk-related symptoms improved 6 months after UAE, but prompted consultation 18 months later when an enlarged uterus and multiple leiomyomas with evidence of infarction—except in the case of a new lateral left leiomyoma—were found by pelvic US. The patient refused both a repeat UAE procedure and hysterectomy.

A 50-year-old patient had heavy bleeding and bulk-related symptoms and presented with two large vascular anterior leiomyomas, each measuring 85 mm in diameter on pelvic US. The patient's condition improved after UAE. Within a year, the leiomyomas had decreased in size to 60 mm and 50 mm and were avascular. However, 2 years after UAE, the patient reported heavy bleeding. Pelvic US revealed the presence of a new vascular 61-mm

leiomyoma in addition to the previous avascular leiomyomas, now measuring 85 mm and 32 mm. The patient refused a repeat UAE procedure and a hysterectomy was performed. The pathology report noted total hyaline degeneration in the two previous leiomyomas but not in the new leiomyoma, a foreign body reaction around many intramyoma vessels, and florid adenomyosis.

The five submucosal leiomyomas were encountered in women who had a history of heavy menstrual periods. Previously, they had shown only vascular intramural leiomyomas confirmed by pelvic US. The patients' condition improved after UAE but intracavitary formations on US control and recurrence of initial symptoms prompted hysteroscopic resection at 6, 14, 30, 40, or 50 months. Symptoms improved after resection. Follow-up was pursued. Hysterectomy was not indicated.

DISCUSSION

The results of this study establish that, after a median follow-up of 30 months, outcome is satisfactory in most cases. Fourteen failures (16.5%) were encountered: six immediate failures, among which was a case of endometrial cancer, and eight late failures or recurrences (a recurrence rate of 10%). Recurrence has rarely been reported in large series of patients. Walker et al (21) reported 23 cases of clinical failure or recurrence (6%) during a mean clinical follow-up of 16.7 months. However, the data in this study show that most recurrences will occur after 20 months.

Hypotheses to Explain Recurrence

Particle size and type.—The polyvinyl alcohol (PVA) particles used in this study are irregular in shape and differ widely in size (150–250 μm). These small particles probably induce ischemia and a gradual reduction in myoma size rather than sudden and massive tumor necrosis. Pathological examination shows that they partially occlude the artery (21). Complete occlusion would result from the thrombus formed in response to the presence of the PVA particles but the embolic material might be redistributed minutes or hours later and flow

restored (22). The largest particles might occlude only proximal leiomyoma vessels and permit collaterals to bypass the occlusion. This could be the explanation for one of the recurrences in this study, with secondary evolution of an interstitial leiomyoma. Nevertheless, the data are not sufficient evidence to incriminate small particle size in recurrence rate. For this, a comparative study of the rate and location of recurrences with different materials is needed. The authors have now switched from PVA particles to large (500–700 μm) well-calibrated collagen-coated acrylic microspheres, which are almost perfectly spherical in shape and occlude the artery totally (23). Their use might help improve reproducibility and also help us understand the underlying mechanisms.

Embolization infarcts leiomyomas but preserves normal uterine tissue.—Shrinkage of existing leiomyomas does not prevent the uterus from developing new leiomyomas. The difference in the vascular networks of leiomyomas (terminal artery) and normal myometrium (large capillary network) accounts for the preferential target of the injected particles being the leiomyoma. Intramyoma vascularization disappears as early as 3 months after UAE but uterine vascularization is maintained as evidenced by contrast enhanced ultrasound (5,24). This is probably due to the presence of collateral pathways. As shown by Razavi et al (17), delineation of ovarian artery to uterine artery anastomosis can be of practical relevance in identifying those patients who would be at risk of UAE or ovarian failure.

Submucosal location of leiomyomas.—The absence of endometrial necrosis after embolization might indeed explain some of the recurrences in this study. Five of the seven new leiomyomas were located in the cavity and were submucosal. None of these patients had undergone hysteroscopy before UAE but no submucosal leiomyomas had been detected on pre-UAE US. Hysterosonography might have been useful. Although the data do not justify excluding submucosal myomas from embolization, it is recommended that patients with submucosal pedunculated leiomyomas undergo hysteroscopic resection in combination with

UAE. Resection can be performed during pre-UAE diagnostic hysteroscopy. Complications were noted after UAE for seven out of 29 pedunculated myomas passed vaginally (25). During the passage of the myomas, menometrorrhagia, pain, and sometimes purulent discharge occurred. Patients should be warned of such possible complications.

Unsuspected associated diseases.—Adenomyosis is a condition often associated with leiomyomas and can worsen symptoms. It may also account for failures. According to the posthysterectomy pathology report, three of the patients had adenomyosis magnetic resonance (MR) imaging, which may prove more useful than sonography for detecting adenomyosis (26). However, in the authors' opinion, suspected adenomyosis is not a sufficient reason to contraindicate embolization.

Finally, unlike hysterectomy, UAE is not a radical treatment (27). Patients must therefore be monitored by clinical and US examinations for more than 2 years after UAE with special attention to the detection of submucosal leiomyomas, possibly by hysterosonography. However, detecting leiomyomas by US is not a reason for altering management in the absence of symptoms. Sonographic controls help evaluate the progression of leiomyomas and compare subclinical recurrence rates.

Since September 2002, the authors' have introduced changes to the embolization procedure: (i) the use of larger (500–700 μm) well-calibrated microspheres; (ii) routinely performing US and MR imaging before the procedure and 6 months after (transvaginal US is as efficient as MR imaging in detecting myomas but less efficient in mapping myomas especially in large [$>375\text{ mL}$ in volume] multiple-myoma [>4 uteri] (28); and (iii) the use of the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire subscales by Spies et al (29) to detect differences in symptom severity and possible recurrences.

In conclusion, although UAE is an effective primary treatment for leiomyomas (82.5% of patients were clinically improved), this study recorded a recurrence rate of 10%. Recurrences occurred mostly after 2 years and not all could be explained. Longer follow-up and more events are

needed to define risk factors for recurrence. Clinical and US examinations are needed before UAE to eliminate pedunculated submucosal leiomyomas and cancers and for more than 2 years after UAE to monitor patients' progress.

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