

Long-term Outcome from Uterine Fibroid Embolization with Tris-acryl Gelatin Microspheres: Results of a Multicenter Study

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PURPOSE: To determine the long-term outcome of uterine fibroid therapy (UFE) using tris-acryl gelatin microspheres (TAGM).

MATERIALS: This was a multicenter prospective study of patients undergoing UFE with TAGM, and during this phase of the study, the clinical outcomes 3 years after treatment were assessed. Measures of outcome included the Ruta Menorrhagia Questionnaire, patient self-assessments of symptoms and impact on activities, patient satisfaction and health-related quality of life as measured by the SF-12. Long-term re-intervention rates were also assessed. The data were analyzed at each interval compared to baseline using appropriate statistical tests.

RESULTS: Of the 102 patients enrolled, 96 patients had complete baseline data and of these, 69 (72%) had known outcomes at 3 years after treatment. Sixty-one patients (64%) completed long-term follow-up without major intervention. An additional 8 patients (8.3%) underwent fibroid surgery (7 hysterectomies and 1 myomectomy). Among those without intervention, at 3 years after treatment, the mean Ruta Questionnaire Score was 19.3, compared to 47.9 at baseline and 24.5 at 3 months ($P < .01$). At baseline, 57% of patients had extremely heavy bleeding, while only 2% had that complaint at 36 months. At 36 months, much or moderate improvement in pelvic pain occurred in 83% of patients, pelvic discomfort in 83%, and urinary problems in 69% and 84% were moderately or very satisfied with their outcome.

CONCLUSIONS: Over the long-term, UFE using TAGM is effective and safe, with high levels of durable symptom control, improved health-related quality of life and patient satisfaction.

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Abbreviations: FIBROID = Fibroid Registry for Outcomes Data, PVA = polyvinyl alcohol, UFE = uterine fibroid embolization

IN recent years, uterine fibroid embolization (UFE) has become accepted as safe and effective in controlling the

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symptoms caused by uterine fibroids. Several studies have confirmed the effectiveness of uterine embolization at 12 months after treatment (1–4). There are also recent studies published that begin to address the question of longer-term outcome (5,6), although these longer-term data are from patients in whom polyvinyl alcohol (PVA) particles or gelatin sponge was the embolic material used.

Tris-acryl gelatin microspheres (Embosphere Microsphere; Biosphere Medical, Rockland, Mass) were cleared for use in the United States by the U.S. Food and Drug Administration in 2000, with clearance specifically for UFE in December of 2002. It is the first embolic material to receive that designation in the United States. There is considerable experience with the ma-

terial now, with publication of results from a number of short- and mid-term studies (7–9). There are little data, however, about the long-term outcome of using these microspheres for UFE.

As a part of the original evaluation of this product, a study was undertaken that compared the outcomes with UFE and hysterectomy for 1 year after embolization. The results for the comparative portion of the study were published in 2004 (10). Although follow-up in the patients who underwent hysterectomy ended at 12 months, the patients who underwent embolization continued to be followed up for 3 years. The outcomes from that cohort of patients after completion of follow-up are presented in this report.

MATERIALS AND METHODS

A detailed presentation of the methods has been previously published (10). The long-term follow-up portion of this study continued only for those who had undergone embolization. Each patient gave their consent for 3-year follow-up, and each participating site's institutional review board approved the protocol.

This was a prospective nonrandomized study of patients undergoing uterine embolization in seven centers in the United States. All patients were determined at the initiation of the study to be premenopausal, between the ages of 30 and 50 years, inclusive, with symptomatic fibroids. Because the long-term outcome was primarily based on the control of menorrhagia, each patient must have had heavy menstrual bleeding at baseline. Heavy menstrual bleeding was determined by subjective patient self-report and not based on questionnaire score. Patients were excluded if they had submucosal fibroids with more than 50% of their diameter within the uterine cavity or if they had a dominant pedunculated subserosal fibroid. Initial imaging was completed by using either ultrasonography or magnetic resonance (MR) imaging. The vascularity of the fibroids—either before or after embolization—was not evaluated as a part of the study. The uterus and dominant (largest) fibroid were measured at baseline and at follow-up imaging performed at 3 and 6 months. These results were reported previously and are not included herein. No study-related imaging was performed more than 6 months after the procedure.

Complications were reported in the initial report and are not included herein. Subsequent interventions, including hysterectomy, myomectomy, and repeat embolizations, were recorded.

Clinical measures of outcome were obtained at 3, 6, 12, 24, and 36 months after treatment. For symptom change as a result of therapy, several measures were used. A pictorial blood loss assessment chart was used for the early portion of the study, but those results were reported earlier and will not be repeated in this report. A menorrhagia questionnaire developed by Ruta et al (11) was also used at baseline and at each follow-up interval. Pa-

tients were also asked to rate the severity of their menstrual bleeding at each interval and the effect their fibroids had on their daily activity both during and between periods. The patients were given an additional questionnaire in which a 7-point scale (much worse through much better) was used to rate changes in menstrual bleeding, pelvic pain, pelvic discomfort, urinary dysfunction, and satisfaction with outcome. In addition, the SF-12 generic quality of life questionnaire was administered at each interval.

Summary statistics were used to assess the data and comparisons made with *t* tests, paired *t* tests, and sign tests. Statistical significance level was set at .05.

RESULTS

Of the original 102 patients, 96 had complete data at baseline and were eligible for long-term follow-up. The final patient was treated in September 2001. Follow-up data at each interval were available for the following numbers of patients: 88 at 3 months, 88 at 6 months, 82 at 12 months, 73 at 24 months, and 61 at 36 months. Follow-up was discontinued at intervention in any patients requiring hysterectomy, myomectomy, or repeat embolization, which accounts for an additional eight patients. Thus, known outcomes are available from 69 of the 96 patients (72%). Not all patients, however, provided all outcome measures at the final follow-up interval, and the numbers providing follow-up are detailed in each of the tables provided.

The results from the menorrhagia questionnaire are presented in **Table 1**. Only 48 patients completed this questionnaire at 36 months, and paired data were available from only 41 patients. However, the results show a substantial and statistically significant improvement in scores (with lower scores being better), and the mean scores remained improved for the duration of the study. These findings are well aligned with the patient self-assessment of menstrual bleeding (**Table 2**). At baseline, 54% of patients rated their bleeding as extremely heavy and 42% rated their bleeding as moderately heavy. During the 36-month follow-up, only 3% or less rated their bleeding as

extremely heavy and less than 28% of patients complained of moderately heavy bleeding. At 36 months after treatment, 22% of patients noted that they were not having periods.

Bulk symptoms of pain, discomfort, and urinary problems (**Table 3**) were substantially improved in most patients, although a smaller number of patients had substantially improved urinary symptoms at each of the data intervals.

Quality of life was measured with the SF-12 questionnaire, and the results are presented in **Table 4**. This 12-question questionnaire is scored and normalized to a mean score of 50 and a standard deviation of 10 for the general U.S. population in 1998 (12). The mean physical and mental summary score for patients before embolization was 45. The physical summary score increased to 51.8 by 3 months and to 53.7 by 36 months, whereas the mean mental score was 52.1 at 3 months and 53.3 at 36 months. The patient's perception of health status correspondingly increased, from a mean of 69.5 to 86.3 by 36 months. At the conclusion of the study, 84% of patients were very or moderately satisfied with the symptom control from the procedure.

During the course of follow-up, eight of the 96 patients (8.3%) underwent fibroid surgery (seven hysterectomies and one myomectomy). There were no repeat embolizations. Specific indications for the repeat interventions were not recorded.

DISCUSSION

The short-term outcome of UFE, including efficacy and safety, have been well documented in single-center case series (2,4,13) and in broader practice, such as the Fibroid Registry for Outcomes Data (FIBROID) (14,15). These demonstrate that a high proportion of patients have a significant improvement in symptoms of heavy menstrual bleeding and bulk-related symptoms. The complications have been reported in one large single center (16) and in the multicenter FIBROID (15); less than 3% of patients have complications necessitating either hospitalization or repeat intervention. Most complications are minor, requiring only medication, or are self-limited. A recent comparative study did show a

Table 1
Results of the Menorrhagia Questionnaire

Data Evaluated	Before Treatment (n = 96)	After Treatment				
		3 mo (n = 83)	6 mo (n = 83)	12 mo (n = 78)	24 mo (n = 67)	36 mo (n = 48)
All data						
Mean score ± standard deviation	47.9 ± 13.1	24.5 ± 13.1	21.03 ± 11.9	17.1 ± 10.1	19.7 ± 11.8	19.2 ± 11
Range	14.29–83.33	7.1–64.3	7.1–64.3	2.4–61.9	0–54.8	0–57.1
Paired data (n = 41)*						
Mean score ± standard deviation	45.2 ± 13.5	22.9 ± 10.7	18 ± 8.6	18.6 ± 11.7	17.8 ± 9.4	20.1 ± 10.7
Range	14.3–83.3	7.1–54.8	7.1–52.4	2.4–61.9	0–54.8	0–57.1

Note.—The difference between the scores at each time interval and that at baseline were statistically significant ($P < .001$). P value was calculated with t tests, paired t tests, and sign tests.

* Paired data are from those patients who had data available at each follow-up interval ($N = 41$).

Table 2
Patient Assessment of Menstrual Bleeding

Description of Bleeding	Before Treatment (n = 95)	After Treatment				
		3 mo (n = 87)	6 mo (n = 88)	12 mo (n = 83)	24 mo (n = 71)	36 mo (n = 59)
Extremely heavy	54 (57)	3 (3)	3 (3)	1 (1)	2 (3)	1 (2)
Moderately heavy	40 (42)	38 (44)	25 (28)	17 (20)	17 (24)	14 (24)
Normal	1 (1)	27 (31)	37 (42)	38 (46)	33 (46)	22 (37)
Light	0 (0)	13 (15)	18 (20)	21 (25)	15 (21)	9 (15)
No periods	0 (0)	6 (7)	5 (6)	6 (7)	4 (6)	13 (22)

Note.—Data are given as numbers of patients. Numbers in parentheses are percentages.

Table 3
Bulk Symptom Status: Proportion of Patients with Moderate to Substantial Improvement after Embolization

Symptom	Time after Embolization				
	3 mo (n = 86)	6 mo (n = 87)	12 mo (n = 81)	24 mo (n = 73)	36 mo (n = 59)
Pelvic pain	63 (73)	68 (78)	77 (83)	60 (83)	49 (83)
Pelvic discomfort	61 (71)	71 (82)	67 (81)	61 (83)	49 (83)
Urinary problems	46 (53)	58 (66)	56 (69)	44 (62)	42 (69)

Note.—Data are given as numbers of patients. Numbers in parentheses are percentages.

higher technical failure rate, a higher minor complication rate in the first 6 weeks after treatment, and a higher repeat admission rate for UFE when compared with hysterectomy (17). That study showed no difference in major complications.

Until the past few years, little has been known about the long-term outcome of UFE. A small retrospective series regarding the outcome after UFE with PVA particles versus myomectomy at 3 years has been pub-

lished (18). In that study, 51 patients who underwent embolization and 30 patients who underwent myomectomy were compared at a minimum of 36 months after treatment. For those patients not needing additional intervention, there were similar levels of symptom improvement and patient satisfaction. However, the repeat intervention rate was higher for patients who underwent embolization than for those who underwent myomectomy (29% vs 3%, $P = .004$).

More recently, results of a 5-year study were reported (6). In that study, 200 patients were treated, all with PVA particles. The results revealed a high level of symptom control, with 73% of patients still improved at 5 years. There was recurrence in 20% of patients, with 13.7% of patients undergoing a hysterectomy. In those patients without intervention, satisfaction remained high. In March of 2006, a group of 96 patients treated with gelatin sponge was reported by Kat-

Table 4
Results of SF-12 Questionnaire with Regard to Overall Health Status and Satisfaction with Outcome

Parameter Evaluated	Before Treatment (n = 96)	After Treatment				
		3 mo (n = 88)	6 mo (n = 88)	12 mo (n = 82)	24 mo (n = 73)	36 mo (n = 61)
Physical status						
Mean score ± standard deviation	45 ± 8.3	51.8 ± 6.7	52.4 ± 6.2	53.6 ± 5.9	52.5 ± 6.3	53.7 ± 5.1
Range	26–61.6	22.3–58.5	23.3–62.6	23.1–64.1	24.8–59.8	30.7–62.8
P value		<.001	<.001	<.001	<.001	<.001
Mental status						
Mean score ± standard deviation	45 ± 11.5	52.1 ± 7.7	52.9 ± 7.9	52.6 ± 7.8	53.8 ± 7.7	53.3 ± 7.4
Range	22.3–63.4	23.8–61.6	20.5–60.8	23.2–61.7	21.8–64.3	25.2–63.1
P value		<.001	<.001	<.001	<.001	<.001
Overall health status						
Mean score ± standard deviation	69.5 ± 19.1	82.6 ± 14.2	85.1 ± 11.3	86.4 ± 14.2	83.9 ± 15.3	86.3 ± 11.2
Range	0–100	28.7–100	43.8–100	0–100	0–100	48–100
No. of patients who were moderately or very satisfied		78 (89%)	78 (89%)	84 (91%)	64 (88%)	52 (85%)

sumori et al (5), who demonstrated an 89% cumulative success rate for those followed up for 5 years. The mean follow-up among those patients was 37 months. The cumulative failure rate at 3 and 5 years was 12.7%, which are similar to those reported in earlier long-term reports.

In these studies, the embolization procedures were completed with PVA particles or gelatin sponge, neither of which are the most common embolic material in current use. On the basis of the FIBROID Registry, most embolization procedures in the United States are currently performed by using tris-acryl gelatin microspheres (15). It is important to document the long-term efficacy of each approved embolic material, given the published data indicating that outcome may vary on the basis of type of embolic material (19). Therefore, the long-term outcome in patients treated with tris-acryl gelatin microspheres is important to determine, and this was the aim of our study.

We found a very high rate of continued symptom control in those patients who completed follow-up. Most patients had dramatic and sustained improvement in menstrual bleeding and bulk symptoms. The measures of health-related quality of life were increased from below the norm to above the norm, and patient's self-assessment of their health status was also high. The rate of repeat intervention is similar to that noted in earlier studies with other materials. These findings

all support the effectiveness of this material as an embolic agent for UFE.

This study is among the first to measure quality of life by using the SF-12, which is a generic quality of life instrument. In addition, it is among the first to measure long-term quality of life after UFE. Given that the SF-12 questionnaire consists of only 12 questions, it would be presumed to be relatively insensitive to small disease-specific changes in health status. It is therefore somewhat surprising to see the extent of the improvement of the questionnaire scores that are sustained over time. This suggests a robust improvement in the broad health status for these women as a result of this therapy.

Much of current opinion on embolic use, including the various types and appropriate sizing, is based on empiric experience or animal studies. Only a few studies in which the clinical and imaging outcomes are compared are based on randomized studies. The first randomized study (20) was published in 2004 and compared tris-acryl gelatin microspheres to PVA particles. The investigators found no difference in fibroid infarction rates or short-term clinical outcomes. A second similar study (19) compared tris-acryl gelatin microspheres to spherical PVA particles and did show a substantial difference in fibroid infarction rates, with much lower rates of fibroid infarction for spherical PVA particles compared to tris-acryl gelatin microspheres. To our knowledge, there are

no randomized studies that compare the use of the various sizes of embolic material(s).

There are limitations in our study. The most important is the loss of some patients to long-term follow-up, with known outcomes in 72% of patients. The primary outcome measures for this study were obtained at 6 and 12 months after treatment and, perhaps as a result, the willingness of patients to continue long-term follow-up may have diminished after that point. Because embolization was considered to have failed in eight patients due to subsequent intervention, there are data available for analysis in even a smaller number of patients (61 of 96 [64%]) and complete data sets for all follow-up intervals in even fewer patients. This rate of follow-up is lower than that of other long-term studies, with 83% of patients undergoing long-term follow-up in one similar study (5) and 90% of patients undergoing long-term follow-up in another (6). Thus, the results must be interpreted with caution and it should be recognized that additional studies may be required before definitive conclusions can be reached.

Another limitation of this study was the lack of long-term imaging follow-up, a weakness also shared by the other reported long-term studies. If performed, contrast media-enhanced MR imaging may have shed light on fibroid infarction rates, and this has been suggested as one surrogate measure of long-term outcome (21). As

with many of the longer-term studies that have been published, however, this study was begun before the importance of imaging findings on long-term outcome was appreciated and, thus, long-term imaging follow-up was not included in the study design.

Despite these limitations, this study provides new data with regard to broad improvements to long-term health status in women undergoing UFE. Furthermore, our results suggest that UFE with tris-acryl gelatin microspheres is effective and durable, with outcomes comparable to those reported in other long-term studies with other embolic material.

References

- Hutchins F, Worthington-Kirsch R, Berkowitz R. Selective uterine artery embolization as primary treatment for symptomatic leiomyomata uteri. *J Am Assoc Gynecol Laparosc* 1999; 6:279–284.
- Pelage J, LeDref O, Soyer P, et al. Fibroid-related menorrhagia: treatment with superselective embolization of the uterine arteries and midterm follow-up. *Radiology* 2000; 215:428–431.
- Spies J, Ascher S, Roth AR, Kim J, Levy EB, Gomez-Jorge J. Uterine artery embolization for leiomyomata. *Obstet Gynecol* 2001; 98:29–34.
- Walker WJ, Pelage J. Uterine artery embolisation for symptomatic fibroids: clinical results in 400 women with imaging follow up. *Br J Obstet Gynaecol* 2002; 109:1262–1272.
- Katsumori T, Kasahara T, Akazawa K. Long-term outcomes of uterine artery embolization using gelatin sponge particles alone for symptomatic fibroids. *AJR Am J Roentgenol* 2006; 186:847–853.
- Spies J, Bruno J, Czeyda-Pommersheim F, Magee S, Ascher S, Jha R. Long-term outcome of uterine artery embolization of leiomyomas. *Obstet Gynecol* 2005; 106:933–939.
- Banovac F, Ascher S, Jones D, Black M, Smith J, Spies J. MR imaging outcome after uterine artery embolization for leiomyomata using tris-acryl gelatin microspheres. *J Vasc Interv Radiol* 2002; 13:681–687.
- Lohle PN, Boekkooi FP, Smeets AJ, et al. Limited uterine artery embolization for leiomyomas with tris-acryl gelatin microspheres: 1-year follow-up. *J Vasc Interv Radiol* 2006; 17:283–287.
- Pelage J, Le Dref O, Beregi J, et al. Limited uterine embolization with tris-acryl gelatin microspheres for uterine fibroids. *J Vasc Interv Radiol* 2003; 14:15–20.
- Spies J, Cooper J, Worthington-Kirsch R, Lipman J, Mills B, Benenati J. Outcome from uterine embolization and hysterectomy for leiomyomas: results of a multicenter study. *Am J Obstet Gynecol* 2004; 191:22–31.
- Ruta D, Garratt Y, Chadha Y, Flott G, Hall M, Russell I. Assessment of patients with menorrhagia: how valid is a structured clinical history as a measure of health status? *Quality Life Res* 1995; 4:33–40.
- Ware J, Kosinski M, Keller S. SF-12: how to score the SF-12 physical and mental health summary scales. 3rd ed. Lincoln, RI: Quality Metric; 1998.
- Spies JB, Ascher SA, Roth AR, Kim J, Levy EB, Gomez-Jorge J. Uterine artery embolization for leiomyomata. *Obstet Gynecol* 2001; 98:29–34.
- Spies J, Myers ER, Worthington-Kirsch R, Mulgund J, Goodwin S, Mauro M. The FIBROID Registry: symptom and quality-of-life status 1 year after therapy. *Obstet Gynecol* 2005; 106:1309–1318.
- Worthington-Kirsch R, Spies J, Myers E, et al. The Fibroid Registry for Outcomes Data (FIBROID) for uterine artery embolization: short term outcomes. *Obstet Gynecol* 2005; 106:52–59.
- Spies J, Spector A, Roth A, Baker C, Mauro L, Murphy-Skrynarz K. Complications after uterine artery embolization for leiomyomata. *Obstet Gynecol* 2002; 100:873–880.
- Hehenkamp WJ, Volkers N, Donderwinkel P, et al. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids (EMMY trial): Peri- and post-procedural results from a randomized controlled trial. *Am J Obstet Gynecol* 2005; 193:1618–1629.
- Broder MS, Goodwin S, Chen G, et al. Comparison of long-term outcomes of myomectomy and uterine artery embolization. *Obstet Gynecol* 2002; 100:864–868.
- Spies JB, Allison S, Flick P, et al. Spherical polyvinyl alcohol versus tris-acryl gelatin microspheres for uterine artery embolization for leiomyomas: results of a limited randomized comparative study. *J Vasc Interv Radiol* 2005; 16:1431–1437.
- Spies J, Allison S, Sterbis K, et al. Polyvinyl alcohol particles and tris acryl gelatin microspheres for uterine artery embolization for leiomyomas: results of a randomized comparative study. *J Vasc Interv Radiol* 2004; 15:793–800.
- Pelage J, Guaou Guaou N, Jha R, Ascher S, Spies J. Long term imaging outcome after embolization for uterine fibroids tumors. *Radiology* 2004; 230:803–809.