Clinical aspects of uterine artery embolization
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CLINICAL ASPECTS OF UTERINE ARTERY EMBOLIZATION

Albert J. Smeets
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ACADEMISCH PROEFSCHRIFT

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aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
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in het openbaar te verdedigen in de Agnietenkapel
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INTRODUCTION
Uterine fibroids are the most common benign tumors in the female genital tract and consist of a proliferation of smooth muscle cells with an extracellular matrix of collagen. Growth of fibroids is influenced by estrogen, progesterone, and a variety of growth factors (1,2). After menopause, fibroids tend to regress. Fibroids may be located in an intramural, submucosal or subserosal position and they may be pedunculated on a thin stalk.

**Incidence of uterine fibroids**

Although the true incidence of fibroids is unknown due to the high prevalence of asymptomatic patients, it is generally reported as 20% to 40% in women of reproductive age (3,4). Black women have three times more often fibroids than white women (5). Most fibroids are asymptomatic, but a substantial proportion of women with fibroids have significant and sometimes disabling symptoms such as heavy menstrual bleeding, pelvic pain and pressure, dyspareunia, and urinary frequency and urgency. Presence of fibroids can reduce the possibility of pregnancy in women attempting conception (6). Symptoms are often of sufficient severity to necessitate surgical intervention; fibroids are the most common indication for hysterectomy. In the United States about 300,000 hysterectomies are performed to remove fibroids each year. In The Netherlands, this figure is estimated to be 5000-8000 hysterectomies per year.

**Treatment**

Since uterine fibroids are benign, treatment is only indicated if symptoms are severe. Medical treatment may consist of analgesics or hormonal therapy. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often effective for the relief of pain and diminish uterine bleeding. Hormonal therapy may include oral contraceptive pills, levonorgestrel containing IUD’s and gonadotropin-releasing hormone analogues. However, long-term benefits of hormonal therapy are questionable (7,8). In addition, many patients have an aversion against hormonal therapy or do not tolerate it well. For patients requiring interventional treatment options include hysterectomy, myomectomy and uterine artery embolization. Selection of treatment modality depends on many factors such as patient’s age, severity of symptoms, comorbidity, wish to future conceive and number, size and location of the fibroids (7,8). Choice of treatment should be tailored to the
specific needs of the individual patient. Hysterectomy is by nature the definitive treatment for fibroids. However, it is a major operation, with an overall complication rate of about 20% (9,10). In addition, hysterectomy may have a negative psychosocial effect by reduced sexual interest, arousal and orgasm, as well as a negative impact on mood and impaired body image (11). Myomectomy with preservation of the uterus can be performed only in patients with fibroids of a certain number, size, and location. Another disadvantage of myomectomy is the substantial risk of fibroid recurrence and the frequent requirement for further surgery (12,13). Therefore, myomectomy is performed less frequently than hysterectomy in The Netherlands.

A relatively new option, uterine artery embolization (UAE), is now available for patients who do not wish to undergo surgery and intervention is considered indicated. UAE was a well-known tool in the treatment of post partum hemorrhage. In 1995 Merland was the first to perform a pre-operative UAE in order to reduce the blood loss during a planned hysterectomy by his colleague the gynecologist Ravina (14). However, it was discovered that after UAE the infarcted fibroids shrank with clinical improvement of patient’s symptoms obviating the need for hysterectomy. In the years to follow UAE developed into a successful tool in the management of uterine fibroids and is nowadays an accepted alternative for surgery. Since UAE is a percutaneous procedure it has two advantages over surgery. It is less invasive (and therefore the recovery time and hospital stay are shorter) and the uterus is preserved, which is not only important for women who wish to conceive (15).

There is some evidence that patients with larger single fibroids and larger uterine fibroid burden may have less improvement and less satisfaction with the results of UAE (16,17). In addition, some fibroids are considered less-than-ideal candidates for embolization such as broad-ligament fibroids, cervical fibroids, small-stalked pedunculated fibroids, and intracavitary fibroids. However, this perception of relative contra-indications is based on clinical experience only without evidence from systematic studies to substantiate these assumptions. The only contra-indications to UAE are pregnancy, suspected pelvic cancer and active pelvic infection. UAE is the therapy of choice in patients who are poor surgical candidates such as obese women or women with previous pelvic surgery.
Arterial supply to the uterus

Most fibroids receive their blood supply from the uterine arteries (Fig. 1). Occasionally the ovarian arteries are additionally involved in uterine blood supply. Anastomoses between the left and right uterine arteries and between the uterine and ovarian arteries are sometimes present. Fibroids are typically surrounded by a dense arterial perifibroid plexus, while the center of the fibroid is hypovascular (18). UAE is aimed to occlude the vessels of the perifibroid plexus inducing ischemic infarction of the fibroid. The devascularized fibroids shrink in several months resulting in relief of symptoms. Pathological studies of uteruses after embolization typically show hyaline necrosis or coagulative necrosis of the tumor mass (19). In general, a successfully treated fibroid will be permanently devascularized. Incompletely infarcted fibroids may grow again and new fibroids may develop over time.

Figure 1. Arterial supply to the uterus and fibroids
MR imaging is used to evaluate the size, location and number of fibroids, both at baseline and at follow-up (Fig. 2).

**Uterine Artery Embolization**

Uterine artery embolization is performed in an angiography suite in the department of Radiology. Via a femoral approach, a catheter is positioned into the uterine artery under fluoroscopic imaging. An arteriogram is obtained to visualize the anatomy of the arterial plexus supplying the fibroids (Fig. 3).

Embolization is then performed by injection of an embolic agent in order to block the vessels of the perifibroid plexus. The embolization is flow directed to the vessels supplying the fibroid. Since the arteries of the perifibroid plexus are much larger than the arteries supplying the myometrium, these vessels are preferentially occluded inducing ischemia of the fibroids only with sparing of the normal myometrium. Embolization is terminated when the vessels of the perifibroid plexus are occluded with sluggish flow in the uterine artery. Then, the procedure is repeated in the contralateral uterine artery (Fig. 4).

![Figure 2. MR before and after UAE.](image-url)
Figure 3. Pre UAE angiogram.

Figure 4. Post UAE angiogram.
After the procedure, most patients have moderate to intense pelvic pain that requires treatment with intravenous narcotics and NSAIDs. Patients also may have malaise, fatigue, and myalgias for several days. About a third of patients develop a mild fever. Most patients return to normal activities within 2-3 weeks after the procedure. Many patients will have light vaginal bleeding, spotting, or a brownish vaginal discharge for several days. Menstrual bleeding, pelvic pain, pressure, and urinary symptoms are usually reduced by the second or third menstrual cycle (20,21).

**Adverse effects of UAE**

The most common combination of symptoms during recovery is the so-called post embolization syndrome (PES) consisting of pelvic pain, mild fever, and general malaise. The syndrome can usually be managed with analgesics and antipyretic agents. Although prophylactic antibiotics are routinely administered before embolization, infection occasionally occurs. It is important to distinguish PES from infection, which is a less common but potentially serious complication (22,23). No deaths have been reported in any of the large clinical studies (20,24,25). Vaginal expulsion of a fibroid or of fibroid tissue occurs in 2-8% of women after UAE, and in some cases surgical extraction may be necessary. Transient or permanent amenorrhea as a result of partial non-targeted embolization of the ovaries occurs sporadically, especially in women of perimenopausal age. Other non-targeted embolic complications have been very rare and include ischemic damage to the bladder, vagina or vulva (26,27).

**Clinical results of UAE**

Since the introduction of UAE in the 90’s of the last century, a number of large observational studies have been performed (20,24,28,29). These studies have shown that heavy menstrual bleeding, pelvic pain, pressure, and urinary symptoms improve in the vast majority of patients.

The EMMY Trial (Uterine Artery Embolization versus Hysterectomy for Uterine Fibroids) was a multicenter, randomized trial in which embolization was compared with hysterectomy in 177 patients in The Netherlands (15,30). After embolization, patients
recovered more rapidly with shorter hospital stay than after hysterectomy. Improvements in health related quality of life was substantial and similar after both therapies. However, a quarter of patients who were embolized had recurrent symptoms that subsequently necessitated hysterectomy. The REST Trial (Randomized Trial of Embolization versus Surgical Treatment for Fibroids) was a multicenter study of 157 patients who were randomly assigned to surgery (hysterectomy or myomectomy) or embolization (31). Health related quality of life after both treatments was similar, although after surgery a greater reduction in symptoms was reported. After a median follow-up of 32 months, a fifth of embolized patients were additionally treated for the same or recurrent symptoms. Another long-term follow-up study also showed that by 5 years after treatment, a fifth of patients who were embolized required repeated intervention (32). Altogether, these studies show that in patients with uterine fibroids symptom relief and health related quality of life is similar after UAE and surgery. However, a fifth to a quarter of patients treated with UAE need additional treatment during follow-up.

American and European guidelines

The American College of Obstetricians and Gynecologists concludes, based on level A evidence that UAE is a safe and effective option for appropriately selected women who wish to retain their uteri. The College also recommends caution when considering embolization in women who desire to retain their ability to conceive, because age-related amenorrhea can occur in a small minority of patients and because there is a possibility of abnormal placentation (33). The Society of Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe state that UAE is indicated for the presence of uterine fibroids that are causing significant lifestyle-altering symptoms, specifically mass effect on the bladder or intestines, and/or dysfunctional uterine bleeding that is prolonged, associated with severe dysmenorrhea, or is causing severe anemia (34).
Aim of this thesis

In the previous section we explained current general concepts of UAE. Although UAE is now widely accepted as a treatment modality for women with symptomatic fibroids, based on the published randomized clinical trials, many technical and clinical issues still are not fully clarified. The aim of this thesis is to address some of these pending issues.

A technical consideration in UAE is the endpoint of embolization. A complete occlusion of the uterine arteries as an endpoint might be needed for adequate infarction of the fibroids but this technique is prone to the occurrence of ischemic complications by inadvertent occlusion of normal arteries to the uterine stroma, ovaries and vagina. On the other hand, a more limited embolization endpoint leaving the ascending segment of the uterine artery open to prevent ischemic damage to normal structures, might result in insufficient infarction of the fibroids. The technique of this limited embolization and the clinical results will be investigated.

Another technical consideration is the embolic agent that is used. While in earlier studies mostly polyvinyl alcohol particles were used, these particles caused catheter blockage in a substantial proportion of procedures. The newer gelatin microspheres were introduced for easier handling without blockage of the catheter. We will evaluate the clinical and imaging results of patients treated with a new type of gelatin microspheres.

Although UAE provides good clinical results on the short-term, the results on the long-term are not firmly established. We will assess the mid- and long-term clinical and imaging results of large cohorts of women treated with UAE.

Although UAE is suitable for most patients with fibroids, there are several factors that are considered contra-indications by some but disputed by others that have never been evaluated. We will assess results of UAE in patients with pedunculated fibroids, in patients with an IUD in situ and in patients with a large fibroid burden.
In summary, this thesis tries to find answers on the following questions:

1. Does limited uterine artery embolization provide sufficient clinical results?
2. Do the new gelatin microspheres as embolic agent offer comparable clinical results than with conventional particles?
3. Are the good short-term clinical results of UAE sustained on the mid- and long-term?
4. Should the presence of pedunculated fibroids be considered a contra-indication for UAE?
5. Should an IUD be removed prior to embolization?
6. Should we refrain from UAE in patients with a large fibroid burden?
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Lampmann LE, Smeets AJ, Lohle PN.
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UTERINE FIBROIDS:
TARGETED EMBOLIZATION,
AN UPDATE ON TECHNIQUE
Abstract

Uterine Fibroid Embolization has become an attractive alternative therapy for symptomatic uterine fibroids. Since the introduction the applied embolization technique underwent several refinements. First complete blockage of both uterine arteries was the goal to obtain complete fibroid devascularization. Lately more sophisticated targeted embolization of the fibroid itself (preserving cervical branches, vaginal branches and ovarian anastomosis) has been carried out by more and more interventionalists. Meanwhile the utilization of calibrated embolic agents has become more and more popular. In this article we will provide the reader an update on the modern uterine fibroid targeted embolization technique, including a summary of catheterization related problems, flaws and tricks.
Introduction

Embolization therapy has been routinely carried out by many radiologists since the last 30 years for the treatment of various diseases and conditions such as bleedings, arterio-venous malformations or fistulae, aneurysms and benign as well as malign tumours.

Uterine fibroid embolization (UFE) however is a relatively new topic, since the first publication on UFE concerning a group of patients treated at Lariboisière Hospital in Paris was published in 1995 (1-2). Different technical approaches of UFE have been extensively described in literature (3-8). The main issue is superselective bilateral catheterization of the uterine arteries and flow-directed injection of embolic agents into the uterine arteries to obtain blockage of fibroid vasculature. The goal is to obtain complete fibroid devascularization in one session with minimal complications and side effects as well as a successful clinical outcome. There still exist many differences in applied embolization technique between centers. Many authors used to advocate catheterization of the uterine arteries directly with 5-French catheters while others are used to manage the uterine arteries mainly with microcatheters and advocate an ipsilateral or bilateral femoral approach (2-8). The utilization of calibrated spheres is becoming more and more popular but the ideal type and size of embolization material is still subject to further evaluation and discussions (9,25).

Technical aspects of UFE in terms of catheterization and embolization procedure

The right common femoral artery is usually punctured after local anaesthesia and a 4 or 5-French introducer sheath is placed. A 0.035 inch angled hydrophilic guidewire (Terumo Europe, Leuven, Belgium) together with a braided 4-French hydrophilic-coated Cobra-shaped (C2) selective catheter (Cordis Europe, Roden, the Netherlands) is manoeuvred over the top into the contralateral iliac system (3,4,8,10). In case of a steep aortic bifurcation and/or elongated aorta-iliac vasculature utilization of a 5-French hook catheter (Cordis Europe, Roden, the Netherlands) may be useful. The contralateral internal iliac artery is catheterized under fluoro or roadmap guidance. In case of a non-conclusive roadmap digital substruction angiography (DSA) is performed in order to identify the origin of the uterine artery. It is extremely important to refrain from DSA series as much as possible and stick to proper collimated roadmap-guided
manipulations in order to avoid extensive ovarian radiation exposure. The 4-French catheter is advanced over the wire into the anterior division of the internal iliac artery and, using road-mapping technique, the uterine artery is carefully selected. The tip of the catheter is next advanced into the horizontal part of the uterine artery, ideally distal to the origin of cervico-vaginal branches. DSA is performed prior to the embolization procedure itself in order to achieve image data of the pre-embolization vasculature including the presence of any uterine-ovarian anastomoses (11). In many cases we appreciate more or less hampered flow after selective catheter placement. In almost all patients we immediately switch over to coaxial microcatheter technique simply because of the fact that appropriate embolization results can only be achieved by real free flow-directed embolization. The only way to achieve guaranteed fibroid devascularization is injecting embolization material under strict free flow circumstances.

Since the goal is to preserve the uterine, cervico-vaginal and ovarian branches one must consider the fact that the in-fibroid centripetal vessels (<500 micron) are endarteries. The size of the peri-fibroid plexus arteries ranges between 500-1000 micron and the size of the cervico-vaginal and ovarian branches is <500 microns. These differences in artery size provide the rationale for the concept of fibroid-targeted embolization with calibrated embolization material. Spheres larger than 500 micron will trespass vessels of 500 micron in diameter. In other words one is able to preserve cervico-vaginal branches and ovarian anastomoses avoiding post-procedural vaginal dryness and permanent amenorrhea. We utilize coloured calibrated microspheres pre-packed in sterile syringes (Embogold, Biosphere Medical, Roissy-en-France, France). We add 5 cc saline and 10 cc Omnipaque 320 (Amersham Cygne, Eindhoven, the Netherlands) and mix over a three-way stopcock to achieve a stable mixture. Omnipaque is used instead of Visipaque for microcatheter applications because of viscosity aspects. Connection of the stopcock assembly to the hub of the microcatheter provides the possibility to work with a closed system without spill of embolization material. After sufficient embolization of the contralateral uterine artery the same braided C2 catheter is used to select the ipsilateral internal iliac artery after performing the Waltman loop manoeuvre in the aorta (12). A non-braided type catheter will absolutely kink in the distal aorta and can only be used for bilateral procedures. The right uterine artery is managed by pulling back the catheter with the use of a selectively placed guidewire. In almost all cases again a microcatheter is placed in the horizontal
part of the right uterine artery avoiding selective catheterization of cervico-vaginal branches by checking its position with contrast medium injections. Control injections should not be too forceful because malposition in tiny branches might blow-up these vessels. Proper catheter tip position will be followed by the embolization procedure itself. We do not routinely perform an aortic flush angiogram to define the ovarian arteries; only when suspicion of parasitic flow to fibroid tissue arises prior to or during the procedure. During the work-up MR imaging we routinely perform MR angiography providing us with clues concerning parasitic vessels and deviation of normal uterine artery anatomy (5). At the end of the procedure an abdominal view is taken to determine the renal status such as hydronephrosis.

A bilateral femoral approach, with simultaneous embolization of both uterine arteries in order to decrease the amount of radiation exposure, can be used. We have to consider the fact that radiation exposure to the patient is directly associated with technical factors implemented by the interventionalist. Although each patient is unique from an anatomical and consequently angiographic point of view, several variables may cause increased patient dose. One should avoid, if possible, excessive image acquisition, unnecessary image magnification, avoid oblique views, large field of views with inadequate collimation and a large air gap between patient and image intensifier (7,13). Catheterization from the contralateral side using a crossover technique is usually easier to perform and requires less fluoroscopy time in particular with less-experienced radiologists. When both catheters are in place two operators can simultaneously inject contrast medium for imaging and together embolize both uterine arteries. Simultaneous embolization of both uterine arteries is consequently associated with a significant decrease in fluoroscopic time. One has to stress the fact that fluoroscopy accounts for the majority of the absorbed ovarian dose during the procedure (14). In our practice, we are using this two-catheter technique only in young women seeking to conceive.

Flow-limiting spasm is a frequent and serious problem during UFE procedures. Spasm slows down the procedure or may even prevent an adequate targeted embolization. The principle of UFE is based on a preferential free flow of embolic agents towards all fibroids, which means that it is crucial to avoid spasm. Spasm is almost always very well noticed distal to the tip of the catheter. Spasm may also develop, and not be directly appreciated, more proximal in the uterine artery around the catheter shaft only
detectable on fluoroscopy by hampering of the contrast medium flow. When encountering one-sided spasm, it might be wise to switch over to the other side or to leave the catheter in place for several minutes and have a coffee break (8,13). The use of vasodilators such as nitro-glycerine 300 microgram intra-arterially may be helpful for a short period of time but is associated with inconsistent results (8). Catheterization using coaxial technique with selective placement of a microcatheter and pulling back the primary catheter out of the uterine artery is in our opinion the best option. In case of small and/or tortuous uterine arteries it is advised to use a microcatheter leaving the guiding C2 catheter positioned in the anterior division of the internal iliac artery or at the level of the uterine artery origin.

When it is difficult to catheterize the ipsilateral uterine artery or when kinking of the catheter is observed during the Waltman loop manoeuvre technique, a second puncture of the contralateral femoral artery may be wise (13). When the uterine artery originates with an acute angle from the anterior division of the internal iliac artery, we always advised to use coaxial approach to deal with this problem. An alternative is a different shaped catheter tip such as a mamarian configuration providing the possibility to manage an acute angled uterine artery origin. Left and/or right anterior oblique views maybe very helpful to determine the in most cases antero-medial oriented origin of the uterine arteries. Pelage stressed the importance and angiographic consequences of the variant uterine artery anatomy. In 45% of cases the uterine artery is the second branch from the anterior division, in 45% there is a trifurcation with anterior and posterior division, in 8% the uterine artery arises from the obturator artery and 8% from the posterior division (11). In case of a unilateral absence of the uterine artery even a replacement by an enlarged round ligament artery has been described (11,26). We have to consider the extreme importance of instructions concerning medication prior to UFE. Patients should refrain from GnRH analogues for at least 6 weeks prior to the procedure in order to prevent overall arterial and uterine artery spasm during catheterization.

Parasitic fibroid blood supply from ovarian arteries has been reported as the potential cause of failure of UFE (15). Identification of a significant flow from the ovarian artery is possible by pre or post-embolization pelvic flush aortography and/or pre-embolization MR angiography (16). Subsequently superselective catheterization of the ovarian artery
can be successfully performed using a 4-French Cobra-shaped catheter in combination with a microcatheter. A reversed curve of the 4-French catheter after forming a Waltman loop allows easy catheterization of the ovarian artery origin (11). Free flow embolization of the fibroids with larger particles can be performed successfully with the tip of the catheter positioned 3-4 cm distal to the origin of the ovarian artery. In case of ovarian artery supply we however refrain from prompt ovarian artery embolization during the first session. In our experience, in almost all circumstances the primary embolization results are satisfactory and no secondary ovarian artery embolization is needed (16).

**Angiographic end-point**

The standard technique (embolization to stasis) consisted of embolizing until the flow has ceased in the main uterine artery (2-6,8). Injection of embolic agent is stopped when no more proximal arterial flow and/or reflux of contrast material is noticed. Pathology data from pre- and postoperative fibroid embolization cases reveal that the peri-fibroid plexus with artery diameters ranging between 500 to 900 \(\mu\)m is the wanted target for embolization (24,25). Consequently the embolization procedure should come to an end when a so-called “pruned-tree” appearance of the ascending segment of the uterine artery with complete disappearance of the fibroid feeding vessels is observed. During embolization changes in vascular flow can be appreciated such as opening of vessels to the contralateral vasculature and sudden visualization of ovarian anastomoses. We use calibrated spheres sized 500-700 micron in cases without ovarian anastomoses. For women presenting with ovarian branches and women seeking to conceive 700-900 micron sized particles are employed. Our goal is to preserve cervico-vaginal branches, ovarian anastomoses and as many normal uterine vessels as possible. This targeted embolization concept handling this angiographic end-point reveals appropriate clinical success rates preserving ovarian and endometrial function (21,25).

**Embolic agents**

There are currently three embolic agents widely used for UFE: gelatin sponge, non-spherical PVA particles and tris-acryl gelatin microspheres such as Embospheres and Embogold (9).
Gelfoam has been extensively used for 30 years to perform haemostatic embolization. Pledgets manually cut into strips and then rolled and loaded into the nozzle of a 2 cc syringe are particularly suitable for pelvic embolization. This embolic agent is inexpensive and often used for UFE in less prosperous countries (18). Short-term results are encouraging but it may be hypothesized that a higher rate of clinical failures, recurrences and post-embolization sequelae may be expected (18,19).

Non-spherical PVA has been successfully used as an embolic agent in various territories for more than 20 years and for uterine purposes since 1989 (2-9). Non-spherical PVA has certain disadvantages in clinical practice. The material has to be delivered in an adequate suspension but still occlusion of delivery catheters may occur, especially when microcatheters are used (17). After the initial experience of UFE using small PVA particles, most groups have been using 355-500 and 500-700 micron PVA particles (3,4,7).

Until now, a single spherical embolic agent is widely available on the market. These tris-acryl gelatin microspheres have been used in Europe since 1995 in various territories (20,25). In our facility we started to use these calibrated microspheres in 1999 for UFE in order to achieve targeted devascularization of the perifibroid plexus preserving uterine and ovarian vasculature. Microspheres have certainly advantages over non-spherical agents because they neither create proximal aggregation in vessels nor occlude the microcatheters that easy (21). This material can even be delivered through a catheter smaller than their nominal diameter because they are compressible.

We currently utilize the Renegade Hi-Flo microcatheter with an inner lumen of 0.027 inch (Boston Scientific International, La Garenne Colombe, Cedex, France) providing the possibility for an easy injection of 700-900 micron spheres and even the 900-1200 sizes will pass with some effort (22).

Alternatively spherical PVA particles are already available on the market (Contour SE, Boston Scientific International, Watertown, Ma, USA) or will be very soon. There are however not many clinical evidence-based data available yet to prove that either one of these three types of embolization agents is more effective than others in terms of UFE clinical outcome (25). In initial reports of UFE, the injection of PVA particles was followed by the placement of coils or injection of gelatin sponge pledgets to ensure durable occlusion of the uterine artery (2,5,8). Most groups are not currently using any
type of secondary embolization agent. However, in problems during UFE, sometimes alternative embolization material is needed.

Conclusion

In conclusion we have to accept the fact that there are still many questions to be answered, not only considering UFE in general but also from a technical point of view. Although there are not yet many evidence-based data widely available concerning the choice of the most effective and safest embolic agent, we strongly advocate the targeted embolization concept with calibrated spheres. Smaller particles will probably cause more fibroid shrinkage, but may also be associated with an increased risk of complications. Complete occlusion of both uterine arteries may cause unnecessary myometrial, endometrial and ovarian ischemia.

A limited devascularization by targeted embolization of the perifibroid plexus is consequently an attractive and rational approach. Liberal use of microcatheters to guarantee free flow embolization will provide a better devascularization of uterine fibroids than with the larger 4-French catheters because of a reduced incidence of flow-limiting conditions.
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EMBOLIZATION OF UTERINE FIBROIDS WITH POLYZENE F COATED HYDROGEL MICROSPHERES: INITIAL EXPERIENCE
Abstract

Purpose
To evaluate the efficacy and safety of precisely calibrated microspheres (Embozene) for uterine artery embolization (UAE) in women with symptomatic uterine fibroids.

Patients and Methods
Between August 2006 and August 2008, 86 consecutive premenopausal women (mean age 43.9 years, median 44, range 28-54) were treated with UAE. Embolization was performed via a bilateral femoral approach using two microcatheters. Calibrated microspheres of 500, 700 and 900 µm alone or in combination were used as embolic agent. MRI was used to assess the change in uterine and dominant fibroid volume as well as dominant fibroid and overall infarction rate. Clinical follow-up was evaluated by the Uterine Fibroids Severity and Quality of Life questionnaire (UFS-QOL) at baseline, at 3 months and in November 2008.

Results
At 3 months, mean volume reduction of the dominant fibroid and uterus was 45% and 42% from initial mean volume. Mean dominant fibroid and overall infarction rate at 3 months were 95% and 96%. No microcatheter blockage occurred and there were no technical complications. At follow-up, permanent amenorrhea developed in 7 women (8.1%). Four women (4.7%) had additional therapy after UAE; three had a hysterectomy and one was embolized for a second time. The UFS-QOL showed significant (p<0.0001) improvement in both symptom severity and quality of life after 3 months and continued to improve at last follow-up of mean 12.8 months.

Conclusion
The use of precisely calibrated microspheres for UAE is effective and safe. Microcatheter blockage did not occur. Clinical and imaging results are comparable to studies in which other microspheres are used.
Introduction

Uterine artery embolization (UAE) is increasingly used for treatment of uterine fibroids in symptomatic women unresponsive to medical therapy (1-5). Several embolic particles have been used successfully for UAE (6,7). Tight size calibration is considered important for effective embolization of arteries of the fibroids only and sparing the smaller arteries of the uterus. Particles that are larger than indicated on the vial may cause blockage of the catheter or too proximal embolization of uterine artery branches with insufficient infarction of the fibroid. On the other hand, particles that are smaller than indicated may penetrate deep in uterine arterioles with possible ischemic damage to the uterus. It is generally assumed that the optimal particle size for embolization of fibroids while sparing the uterus is 700-900 µm. Precise particle size calibration seems advantageous to avoid technical and clinical complications attributed to aberrant particle sizes (8-11).

In this study, we evaluated feasibility, efficacy and safety of a new biocompatible embolic agent consisting of microspheres calibrated with a narrow bandwidth.
Patients and Methods

Patients
This study was approved by the Institutional Review Board and written informed consent was obtained in all women. Between August 2006 and August 2008 86 consecutive premenopausal women (mean age 43.9 years, median 44, range 28-54) with symptomatic uterine fibroids were included. Seventy-four women presented with heavy menstrual bleeding, 46 with pelvic pain and 43 with bulk-related symptoms. All women were previously treated medically with insufficient clinical results. Before UAE, all patients had a gynecological consultation to confirm that presenting symptoms were caused by uterine fibroids and not by infection or malignancy. Exclusion criteria for UAE were pregnancy, pelvic inflammatory disease, gynecological malignancy, pure adenomyosis and thin-stemmed pedunculated fibroids.

Calibrated microspheres
The embolic material used in this study was Embozene Microspheres (CeloNova BioScience, Newnan, GA, USA). These microspheres consist of a hydrogel core of polymethylmethacrylate and a flexible shell of polyphosphazene: a synthesized inorganic biostable and biocompatible polymer (12,13). The microspheres suspended in contrast material are spherical, flexible and easy compressible. Embozene microspheres are precisely calibrated by sieving with a high uniformity of spheres (Fig. 1). The microspheres are color coded according to size and are available in sizes ranging from 40-1300 µm.

![Figure 1](image.png)

Figure 1. Photomicrograph of Embozene spheres 700 µm. Note uniform size.
**Imaging**

Pelvic MRI (native and gadolinium-enhanced T1 weighted sagittal and axial images) was performed at baseline and at 3 months follow-up. MRI’s were evaluated by 2 radiologists in consensus. Uterine and dominant fibroid volumes were calculated using the formula of a prolate ellipse (length x depth x width x 0.5233). Volume changes were calculated as proportions of initial volumes. Contrast-enhanced T1-weighted images were used to assess the percentage of infarction of the dominant fibroid and the overall uterine infarction by visual estimation of decrease in enhancement as compared to baseline. Infarction rates were classified as 100%, 0-99%, 80-90% and less than 80% (14).

**Embolization procedure**

Embolization was performed under local anesthesia with antibiotic prophylaxis. Via a bilateral femoral co-axial approach two microcatheters (EmboCath Plus, BioSphere Medical, inner lumen 710 µm) were positioned in the horizontal part of both uterine arteries distal to the cervicovaginal branches. Embolization was performed simultaneously on both sides using calibrated microspheres of 500, 700 and 900 µm alone or in combination. Technical success was defined as a complete stop in the ascending part of both uterine arteries (15). The size of calibrated microspheres used was recorded.

**Clinical follow-up**

The standardized and validated Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire (16) was filled out by all patients before UAE, at 3 months and at latest follow-up in November 2008. In addition, adverse events and additional therapies during follow-up were recorded (17).

**Data analysis**

Complications were expressed as a proportion with 95% CI. Mean volume reduction of dominant fibroid and uterus was calculated as a proportion of initial volume. Chi-square test was used for comparison of proportions. P-values <0.05 were considered significant. UFS-QOL questionnaires were evaluated with ANOVA. Statistical analysis was done with MedCalc statistical software (MedCalc, Mariakerke, Belgium).
Results

Embolization procedure
Embolization was technically successful in all 86 patients. In the 172 microcatheters that were used to deliver the microspheres, no blockage occurred (0%, 95% CI 0-1.8%). The microsphere sizes that were used are listed in Table 1. There were no adverse events during the hospital admission for embolization (0%, 95% CI 0-3.7%).

Imaging
Mean dominant fibroid volume before UAE was 185 cm$^3$ (median 123 cm$^3$, range 4-1373 cm$^3$) and at 3 months this was 102 cm$^3$ (median 60 cm$^3$, range 1-647 cm$^3$). Mean volume reduction of the fibroid was 83 cm$^3$ or 45% from initial mean volume. Mean uterus volume before UAE was 541 cm$^3$ (median 479 cm$^3$, range 63-1929 cm$^3$) and at 3 months this was 315 cm$^3$ (median 278 cm$^3$, range 18-1004 cm$^3$). Mean volume reduction of the uterus was 226 cm$^3$ or 42% from initial mean volume. Mean infarction rate at 3 months of the dominant fibroid was 95% (median 95%, range 80-100%). Overall fibroid infarction rate at 3 months was 96% (median 95%, range 70-120%).

Clinical follow-up and additional procedures
Mean follow-up was 12.8 months (median 11, range 3-29 months). Minor complications occurred in 13 women (15%, 95% CI 8.9-24.3%) after UAE: transient amenorrhea developed in 4 women (all > 45 years), one reported vaginal dryness, 6 had transient vaginal discharge, and two had a urinary tract infection that was treated with antibiotics. Major adverse events occurred in 8 women (9.3%, 95% CI 4.6-17.5%): 7 developed permanent amenorrhea (2 were < 45 years) and one had transient ischemia of part of the right labia as a result of too proximal positioning of the microcatheter during particle injection. This last woman recovered completely without therapy.

The results of the UFS-QOL are shown in Table 2. Symptom severity score decreased significantly (p<0.0001) after 3 months and further decreased at last follow-up. Overall quality of life improved significantly (p<0.0001) after 3 months and continued to improve at last follow-up.
Four of 86 women (4.7%, 95% CI 1.5-11.7%) had additional therapy after UAE: one was embolized for a second time one year after UAE due to insufficient symptom relief and persisting enhancing fibroids on MRI. Three women had a hysterectomy: in 2 at 5 and 7 months after UAE because of persisting pain and in one woman hysterectomy was performed after incomplete fibroid expulsion 2 months after UAE.

| microsphere size                  | number of patients |
|-----------------------------------|--------------------|
| 500 µm only                       | 10 (12%)           |
| 500 µm and 700 µm                 | 4 (5%)             |
| 700 µm only                       | 43 (50%)           |
| 700 µm and 900 µm                 | 26 (30%)           |
| 900 µm only                       | 2 (2%)             |
| 500 µm and 700 µm and 900 µm      | 1 (1%)             |

**Table 1.** Microsphere sizes used for uterine artery embolization in 86 patients

|                      | baseline N=86 | 3 months after UAE N=85* | mean 12.8 months after UAE N=82** |
|----------------------|---------------|--------------------------|----------------------------------|
| symptom severity     | 64            | 23                       | 16                               |
| concern              | 50            | 86                       | 92                               |
| activities           | 51            | 84                       | 94                               |
| energy and mood      | 53            | 78                       | 88                               |
| control              | 55            | 81                       | 88                               |
| self-consciousness   | 57            | 83                       | 88                               |
| sexual function      | 58            | 78                       | 85                               |
| overall              | 53            | 82                       | 90                               |

**Table 2.** Mean UFS-QOL score at baseline and during follow-up of 86 women treated with uterine artery embolization for uterine fibroids.

*One patient had a hysterectomy 2 months after UAE

* Four women had additional therapy after UAE

*One patient had a hysterectomy 2 months after UAE

** Four women had additional therapy after UAE
Discussion

This study demonstrates the feasibility, efficacy and safety of a precisely calibrated new embolic agent Embozene for UAE in a large cohort of patients with symptomatic uterine fibroids. Relief of clinical symptoms, volume reduction of uterus and fibroids, fibroid infarction rate, complications and proportion of women needing additional therapy during follow-up was comparable to other studies using different embolic agents (6,7). The Embozene spheres, color coded on particle size, were easy to use. Blockage of the microcatheter did not happen. This indicates that aggregation and clumping of the spheres inside the microcatheter does not occur with the sphere sizes used for UAE.

The new Embozene microspheres are calibrated with a narrow bandwidth. This precise calibration allows a more accurate prediction of the targeted vasculature that will be occluded by the microspheres. A relation between size of the microspheres and the diameter of the vessels that are occluded is established in several experimental and clinical studies of embolization of tumors and arteriovenous malformations (18,19).

Vessel calibre in myometrium and fibroids differ in several ways. The proximal larger arteries in the serosal part of the myometrium branch and taper to smaller arteries penetrating deep into the luminal part (8). The arteries of the perifibroid plexus are larger than the arteries feeding the myometrium (500-1000 µm versus <500 µm). The calibre of the arteries of the perifibroid plexus does not decrease distally (9). When particles are injected through the microcatheter into the uterine artery, almost all particles conglomerate in the larger arteries of the perifibroid plexus and not in the smaller arteries of the myometrium (10,11). This explains the selective ischemic effect of embolization on the fibroids only and sparing the normal myometrium. This selective fibroid devascularisation leads to a decrease of fibroid (and uterine) volume with alleviation of clinical symptoms.

On theoretical grounds the size of the microspheres used for UAE should ideally equal the diameter of the arteries of the perifibroid plexus to achieve a complete and selective devascularisation of the fibroids. Larger sizes microspheres might not penetrate deep enough into the target vessel to induce devascularisation of the fibroid and may cause microcatheter blockage. Smaller microsphere sizes might penetrate too deep with a risk
of necrosis of the normal myometrium. Therefore, the use of an embolic agent with a precise calibration to occlude the perifibroid plexus only seems to be advantageous in terms of better control of the extent of embolization and thus the clinical outcome. The particle size used for UAE should be > 500 µm, the diameter of arteries feeding the myometrium. Probably, the most appropriate size would be 700-900 µm. Whether or not tight calibration of microspheres results in better and more selective fibroid infarction with improved clinical outcome remains uncertain from our data.
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Lohle PN, Boekkooi FP, Smeets AJ, Pieters JJ, Vervest HA, Lampmann LE, Sluzewski M.
J Vasc Interv Radiol 2006;17:283-7
LIMITED UTERINE ARTERY EMBOLIZATION FOR LEIOMYOMAS WITH TRIS-ACRYL GELATIN MICROSPHERES: 1-YEAR FOLLOW-UP
Abstract

Purpose
To assess the safety and efficacy of uterine artery embolization (UAE) using large calibrated tris-acryl gelatin microspheres.

Material and Methods
One hundred fifty-eight women with symptomatic uterine fibroids underwent UAE. Embosphere was used in 105 women and Embogold microspheres in 53 women. Major and minor complications were assessed. At 12 months, relief of symptoms and patient satisfaction were assessed and volume reductions of the uterus and dominant fibroid were calculated.

Results
Median age of the subjects was 43 years (mean, 42.3 y; range, 23-53 y). Preprocedural symptoms were heavy menstrual bleeding in 89%, pain in 64%, and bulk-related symptoms in 57%. At 12 months follow-up, the proportion of women with heavy menstrual bleeding, pain, and bulk-related symptoms had decreased to 9%, 8%, and 8%, respectively. Patient satisfaction was grouped as follows: very satisfied 57%, satisfied 36%, and not satisfied 7%. Mean uterine and dominant fibroid volumes before UAE were 532 cm$^3$ and 201 cm$^3$, respectively. At 12-month follow-up MR imaging, mean uterine volume decreased to 260 cm$^3$ and mean dominant fibroid volume to 78 cm$^3$. These differences were statistically significant (P<0.0001). There were no procedure-related deaths. No emergency hysterectomy was needed. Permanent amenorrhea occurred in 11% of women. Transient amenorrhea occurred in 13% of women, and fibroid expulsion occurred in 10% of women. Twelve women (7.6%) had additional therapy: nine underwent additional embolization and three had hysterectomy.

Conclusion
Targeted UAE using large calibrated microspheres is safe and effective in the relief of symptoms in the majority of patients. At 12 months, a marked fibroid and uterine volume reduction is obtained.
Introduction

Uterine fibroid, or leiomyoma, is the most common solid pelvic tumor in women during reproductive life (1). If symptomatic, hormonal therapy or surgery can be considered (2, 3). In addition to the risks associated with surgical procedures, there may also be emotional drawbacks in women (4, 5). Uterine artery embolization (UAE) is nowadays considered an effective alternative to medical and surgical therapy (6–10). Advantages of embolization over hysterectomy are preservation of the uterus, shorter hospital stay, and quick recovery (11).

In UAE, mainly nonspherical polyvinyl alcohol (PVA) particles have been used, usually aiming at complete occlusion of both uterine arteries (6–9). Targeted UAE with calibrated trisacryl gelatin microspheres (CTGM) is a relatively new technique in which occlusion of the perifibroid plexus is performed, leaving the uterine artery, cervicovaginal branches, and shunts patent. The material has demonstrated good biocompatibility and safety (12, 13). The use of CTGM has been approved by the Food and Drug Administration for UAE in cases of symptomat ic uterine fibroids. In addition, it has been suggested that a less aggressive embolization of the uterine arteries may provide the same clinical success rate with lower complication rates compared to complete uterine artery occlusion using nonspherical PVA (14,15). Short-term results in a limited number of patients embolized with CTGM were favorable (16-19).

We assessed the safety and clinical and radiological efficacy of UAE using large CTGM in 158 consecutive symptomatic women with near-complete follow-up at 12 months.
Material and Methods

Patient Population and Selection Criteria
Between February 2001 and February 2004, 158 consecutive women with symptomatic uterine fibroids underwent targeted embolization using CTGM; 105 women were treated with Embosphere and 53 women with Embogold microspheres (Biosphere Medical, Roissy, France). The choice of embolic agent used was influenced by factors such as operator preference and availability in stock and was independent of patient or fibroid characteristics.

Of the 158 women, 142 were white, 11 Afro-Caribbean, and 5 Asian. Median age was 43 years (mean, 42.3; range, 23-53 y). Inclusion criteria were as follows: women with a uterine fibroid, reporting heavy menstrual bleeding, pain, and/or bulk-related symptoms in whom insufficient clinical results were obtained with previous medical therapy or myomectomy. Exclusion criteria were postmenopausal status, malignancy, pedunculated fibroids, and pregnancy. Women seeking future fertility were not excluded.

Our Institutional Review Board approved this study and informed consent was obtained in all subjects.

Procedure and Angiographic Endpoint of Embolization
Via a right femoral artery approach, the left internal iliac was catheterized with a hydrophilic 0.035-inch guide wire and a 4-F, Cobra C2 shaped glide-catheter. Selective digital subtraction angiography of the anterior division of the left internal iliac artery and uterine artery was performed. A microcatheter was used for small or tortuous arteries and in case of vasospasm.

The Waltman loop manoeuvre was applied to catheterize the right uterine artery. After positioning the (micro) catheter in the horizontal part of the uterine artery, embolization was performed using CTGM of 500 to 1200 µm. Each vial (2 cm³) of microspheres was mixed with 10 mL of contrast medium (Omnipaque) and 5 mL saline to obtain a stable suspension of the microspheres. The angiographic endpoint was defined as a complete occlusion of branches to the perifibroid plexus and sluggish flow in the ascending
segment of the uterine artery, leaving the main uterine artery, cervicovaginal branches, and utero-ovarian anastomoses patent (16). Any intra-catheter aggregation and blockage was recorded.

**Clinical and Imaging Follow-up Protocol**

Major complications, defined as events requiring immediate additional therapy (including emergency hysterectomy), permanent adverse sequelae (including permanent amenorrhea), or death were recorded. Transient amenorrhea, fibroid expulsion, skin rash, and infection requiring nominal therapy were considered as minor complications (20). Additional embolization or elective hysterectomy was considered a failure of initial treatment. At 12 months, evaluation of subjective symptoms and patient satisfaction were assessed by a questionnaire during an outpatient clinic consultation. The patients were asked to categorize their symptoms (bulk-related, pain, and bleeding) into improved or unchanged/worsened. They were asked to score overall satisfaction “very satisfied”, “satisfied” or “not satisfied.” Finally, the subjects were asked to estimate the number of days before returning to routine daily activities after UAE.

Prior to embolization, pelvic MR imaging was performed in all 158 women. The MR imaging protocol consisted of coronal, sagittal and axial TSE-weighted sequences and contrast enhanced sagittal T1 series. Volume calculation was done by using the formula of a prolate ellipse (length x depth x width x 0.5233). Volume reductions of the uterus and dominant fibroid were calculated by comparing volumes prior to embolization with the volumes at the 12-month MR imaging follow-up.

**Statistical Analysis**

Mean, median, range, and standard deviation (SD) of uterine volumes and dominant fibroid volumes were assessed before and after UAE. These differences were compared using the t-test, and P-values less than .05 were considered significant. The following results were compared for women embolized with Embogold versus women embolized with Embosphere microspheres: proportion of patient satisfaction, uterine volume embolized per cubed millimeter of injected microspheres, uterine volume reductions, number of days before returning to routine activities after UAE, the proportion of subjects with fibroid expulsion and skin rash.
Mean, median, range and SD of volume of injected microspheres were assessed and sizes were recorded. The same approach was taken for both types of microspheres. Uterine volume embolized per cubed millimeter of injected microspheres was assessed for both types.

Statistical analysis was performed with the t-test for continuous data and comparison of proportions with the χ² test (MedCalc statistical software, Mariakerke, Belgium). P values less than 0.05 were considered statistically significant.

Results

Immediate Results and Major Complications
Bilateral uterine artery embolization was performed in 152 of 158 women (96%). Failure of catheterization resulted in unilateral uterine artery embolization in 6 of 158 women (4%). Embolization through 4-F C2 catheters alone was performed in 25%, microcatheters alone in 57%, and a combination in 18%. Intracatheter aggregation and blockage did not occur in any of the embolization procedures.

Mean, median, range, and SD of volume of injected microspheres were 8.5 cm³, 6.5 cm³, 2 to 42 cm³, and 6.3 cm³, respectively. There were no procedure-related deaths in the 158 women treated with UAE (0%, 95% CI, 0–2.9%). No events requiring immediate additional therapy occurred and no emergency hysterectomy was required. Permanent amenorrhea occurred in 17 women (11%). All women who developed permanent amenorrhea were 45 years or older.

Minor Complications
After UAE, transient amenorrhea occurred in 20 women (13%) and fibroid expulsion occurred in 16 women (10%) between 4 weeks and 12 months after UAE. Vaginal fibroid evacuation from the uterine cavity by the gynecologist was needed in 5 of these 16 women, without hospitalization. Expelled fibroids were located submucously in 10 and intramurally in 6 women and size ranged between 4 and 13 cm.
Additional Procedures

Twelve women (7.6%) had additional therapy after UAE: nine women underwent secondary embolization and three women had a hysterectomy at 3, 8, and 12 months after embolization. Secondary embolization in the nine women was performed because of recurrent symptoms and acceptance of a second embolization. Hysterectomy was performed for recurrent symptoms in two women, these two refused secondary embolization. In one woman, hysterectomy was performed because of suspected uterine sarcoma but pathological examination showed a fibroid.

Clinical Follow-up and MR Follow-Up

At 12 months follow-up, 12 women (7.6%) had additional therapy after initial UAE: nine women underwent additional embolization and three women had a hysterectomy. So, 146 women were eligible for the 12-month clinical evaluation. Four women of these 146 were lost to follow-up (12-month clinical follow-up rate: 142 of 146, 97%). At 12 months clinical follow-up, resolution or improvement of symptoms in the 126 women initially presenting with heavy menstrual bleeding occurred in 113 women (91%). Resolution or improvement of symptoms in the 91 women initially presenting with pain occurred in 80 women (92%). Resolution or improvement in the 81 women initially presenting with bulk-related symptoms occurred in 70 women (92%). Patient satisfaction in the group of 142 women was as follows: very satisfied 81 (57%), satisfied 51 (36%), and not satisfied 10 (7%). Thirty-two of 158 women did not have a 12-month MR imaging follow-up for the following reasons: additional embolization (9), hysterectomy (3), pregnancy (2), and claustrophobia (1). So, 143 women were eligible for 12-month MR imaging follow-up. Of these 143 women, we were unable to follow-up 4 women, and 13 declined the 12-month MR imaging follow-up (12-month MR imaging follow-up rate: 126 of 143, 88%). Mean, median, and SD of uterine and dominant fibroid volumes as well as volume reduction in 126 women before and 12 months after limited uterine artery embolization are listed in Table 1. In the 126 patients with MR follow-up the median uterine volume before UAE was 465 cm³ and at 12-month follow-up this was 208 cm³. In the 126 patients with MR follow-up the median fibroid volume before UAE was 131 cm³ and at 12-month follow-up MR imaging this was 34 cm³. Using the t-test, these differences were statistically significant (P<.0001).
Prior to UAE 12 Months after UAE Volume Reduction, %

|                                | Prior to UAE | 12 Months after UAE | Volume Reduction, % |
|--------------------------------|--------------|---------------------|---------------------|
| Mean uterine volume, cm³       | 532          | 260                 | 47                  |
| Median uterine volume, cm³     | 465          | 208                 | 49                  |
| SD                             | 375          | 190                 | 34                  |
| Mean dominant fibroid volume, cm³ | 201        | 78                  | 60                  |
| Median dominant fibroid volume, cm³ | 131        | 34                  | 66                  |
| SD                             | 249          | 100                 | 40                  |

Table 1. Uterine and Dominant Fibroid Volumes before and 12 Months after Limited Uterine Artery Embolization (n=126).

*Embosphere versus Embogold Results*

The comparison of relevant characteristics between the use of Embosphere and Embogold microspheres is listed in Table 2. Of 158 women, 105 were embolized with Embosphere and 53 with Embogold.

Uterine volumes before UAE in the two groups did not differ significantly. Of the 142 women with 12-month clinical follow-up, 47 had been embolized with Embogold and 95 with Embosphere microspheres.

The mean volumes of injected Embosphere and Embogold did not differ statistically (P=0.3). Uterine volume embolized per cubed millimetre of injected microspheres did not differ statistically (P=0.9) in the two groups. Of the 126 women with 12-month MR imaging follow-up, 82 had been embolized with Embosphere and 44 with Embogold.
Uterine volume reductions showed no significant difference (P=0.75). The frequency of fibroid expulsion did not differ statistically significantly between women treated with Embogold and those treated with Embosphere microspheres (P=0.94). Transient skin rash occurred more frequently in women treated with Embogold than in women treated with Embospheres (P=0.031). Sixty-four women reported the number of days before returning to routine daily activities after UAE. In 47 women treated with Embospheres, this number was mean 17.6 days, and in 17 women treated with Embogold microspheres, this number was mean 30.0 days. This difference was statistically significant (P=0.004). There was no difference in patient satisfaction in the two groups (4 of 47 unsatisfied for Embogold versus 6 of 95 unsatisfied for Embospheres; P=0.89).

|                        | Embosphere | Embogold | P-value |
|------------------------|------------|----------|---------|
| Number of women        | 105        | 53       |         |
| Mean uterine volume before UAE, mL | 396        | 516      | 0.11    |
| Mean volume (SD) embolic agent used, cm³ | 8.1 (5.2)  | 9.2 (8.0) | 0.30    |
| Uterine volume embolized per cm³ embolic agent, mL | 61.9       | 64.7     | 0.9     |
| Mean uterine volume reduction, % | 46         | 48       | 0.75    |
| Fibroid expulsion, %   | 9.5        | 11.3     | 0.94    |
| Skin rash, %           | 1.0        | 9.4      | 0.031   |
| Days before returning to routine activities | 17.6       | 30.0     | 0.004   |
| Unsatisfied patients,% | 6.3        | 8.5      | 0.89    |

Table 2. Relevant Characteristics of the Use of Embosphere versus Embogold Microspheres
Discussion

In this study with prospective data collection and a high rate of clinical and MR imaging follow-up, we confirmed that UAE using CTGM in symptomatic uterine fibroids has a low risk of procedural complications (6-11). Relief of clinical symptoms, patient satisfaction, adverse events, and uterine and fibroid volume reduction were in the same range as those in studies on the use of PVA (6-11).

The results are also comparable with those of studies reporting on the use of CTGM with shorter follow-up periods (16-19). To date, uterine and fibroid volume reductions after UAE using CTGM have not been published in a large series of patients with 12-month follow-up.

Our results also show the limitations of UAE in the treatment of symptomatic uterine fibroids: 7.6% of patients needed additional therapy and 7% of patients were unsatisfied with the results. Future developments should be aimed at lowering these percentages. The results of the present study show that the effectiveness of limited UAE using large microspheres is comparable to the effectiveness of UAE using nonspherical and smaller particles, as was demonstrated by Spies in a prospective comparative study (15).

The first embolic material used for UAE was nonspherical PVA particles. The usual angiographic endpoint with nonspherical PVA particles was occlusion of the uterine arteries to stasis or near stasis. Embolization was considered complete when a standing column of contrast material was present in the uterine artery or when reflux toward the uterine artery origin was observed. Physical properties of irregular nonspherical PVA particles were thought to be responsible for the tendency to aggregate and for a proximal vessel occlusion with an unpredictable level of occlusion. In addition, aggregation may also result in microcatheter occlusion.

Alternative embolic materials have been introduced, allowing further refinement of the UAE technique. Spherical embolization particles such as CTGM have been developed since 1994 with the aim to overcome the disadvantages of nonspherical PVA particles (13). CTGM was the first spherical embolic agent offering a more uniform and targeted
embolization of the perifibroid plexus. The compressibility of the microspheres made microcatheter clogging a rare event. The so-called limited UAE technique was introduced with a new embolization endpoint: embolization was completed when no residual hypervascularization related to the fibroids was visible, stasis was observed in the distal part of the uterine artery, or reduced flow was achieved in the proximal part of the uterine artery. The main uterine artery, cervicovaginal branches, and utero-ovarian anastomosis (if visible) were left patent, preserving vascularization to normal surrounding tissue, such as myometrium, cervix, vagina, tubes, and ovaries.

Limited UAE with microspheres is more subtle than a nonspherical PVA embolization procedure and requires careful judgment to determine the proper embolization endpoint. CTGM are intended to be injected gradually until complete occlusion of the perifibroid plexus only, maintaining forward flow within the uterine arteries and preserving blood supply to the myometrium. The objective of CTGM fibroid embolization is to achieve complete infarction of all uterine fibroids present while preserving vascularization to normal surrounding tissue. Failure of complete devascularization of the fibroids due to misjudgment of the angiographic endpoint may affect long-term clinical response and may lead to higher recurrence rates. Experience is required to become comfortable with this alternative endpoint. As demonstrated in this study using CTGM in combination with the limited UAE technique, good mid-term results can be obtained. The long-term outcome and possible recurrence of fibroid growth and symptoms are still under evaluation. Long-term studies of larger patient populations are needed to establish the recurrence rate.

To date, there is no consensus on the type and size of embolization materials most effective for UAE. The appropriate technique of embolization in terms of endpoint with each of the available products is the subject of ongoing debate. In our experience, CTGM larger than 500 µm were easy to use in targeted embolization of the perifibroid plexus without compromising the uterine artery. Intracatheter aggregation and blockage did not occur in any of the embolization procedures. This may be due to the more uniform size and different physical and chemical characteristics of CTGM compared to nonspherical PVA (12). Moreover, severe complications reported after embolization with PVA particles such as uterine necrosis, labia necrosis, and infection did not occur (21–26). Our use of CTGM larger than 500 µm may have prevented these
complications. However, permanent amenorrhea was seen in the same frequency range as with the use of PVA (15). In the comparison between Embogold and Embospheres, uterine volume embolized per micrometer injected microspheres, fibroid expulsion, patient satisfaction, and volume reduction did not differ. The occurrence of skin rash was significantly lower in patients treated with Embospheres, as was reported earlier (21). Women treated with Embospheres returned sooner to daily activities than women treated with Embogold. We do not have an explanation for this difference. These findings have led us to refrain from using Embogold in UAE.

In the meantime, the company no longer recommends the use of Embogold for UAE. In conclusion, targeted UAE using CTGM larger than 500 µm is safe and effective in the relief of symptoms in the majority of patients with symptomatic uterine fibroids. After 12 months, a marked fibroid and uterine volume reduction is obtained.
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MID-TERM CLINICAL RESULTS AND PATIENT SATISFACTION AFTER UTERINE ARTERY EMBOLIZATION IN WOMEN WITH SYMPTOMATIC UTERINE FIBROIDS
Abstract

Purpose
To evaluate mid-term clinical results and patient satisfaction following uterine artery embolization (UAE) in women with symptomatic fibroids.

Method
Between August 1998 and December 2002, 135 patients had UAE for symptomatic uterine fibroids. All patients were asked to fill in a questionnaire. Questions were aimed at changes in bleeding, pain and bulk-related symptoms. Symptoms after UAE were scored as disappeared, improved, unchanged or worsened. Adverse events were noted such as vaginal dryness and discharge, menopausal complaints or fibroid expulsion. Patient satisfaction after UAE was assessed. Patient satisfaction of women embolized with polyvinyl alcohol (PVA) particles was compared with satisfaction of women embolized with calibrated microspheres.

Results
The questionnaire was returned by 110 of 135 women (81%) at a median time interval of 14 months following UAE. In 10 women additional embolization or hysterectomy had been performed. Of the 110 responders, 86 (78%) were satisfied with the result of UAE. The proportion of satisfied women embolized with calibrated microspheres was higher compared to women embolized with PVA although this difference was not statistically significant (P=0.053).

Conclusion
UAE in women with symptomatic uterine fibroids leads to improvement of symptoms and patient satisfaction is good in the vast majority after a median follow-up period of 14 months.
Introduction

Uterine fibroids (leiomyomas) are common benign tumors in women of child-bearing age with an incidence of 20-40%. In 10-20% of women these uterine fibroids lead to symptoms such as bleeding, pain and bulk-related symptoms (1). Standard methods of treatment comprise medical treatment or surgery such as myomectomy or hysterectomy. Uterine artery embolization (UAE) was introduced in 1995 by Ravina and Merland (2) as an alternative treatment for women with symptomatic fibroids.

In this retrospective study, we present mid-term clinical results and patient satisfaction after UAE in 110 women with symptomatic uterine fibroids. In the literature there are only limited reports on mid-term clinical results and patient satisfaction after UAE (3-5).

Materials and Methods

General

Prior to embolization, all patients were examined by a gynecologist. All women had symptomatic uterine fibroids with an indication for hysterectomy. All women had undergone one or more of the following treatments without sufficient result: iron supplements, oral contraceptives, various hormone treatments (including GnRH analogues), curettage, endometrium-ablation, myomectomy and homeopathic treatment. Exclusion criteria for embolization were pregnancy, suspected or confirmed gynecological malignancy, avascular calcified fibroids, infection, predominant adenomyosis or thin-stemmed pedunculated fibroids - where the stem diameter is less than 1/3 of the diameter of the fibroid (6).

Informed patient consent was obtained in all women after the embolization procedure was explained including discussing the possible advantages and disadvantages of the procedure, the risks and the expected results. Prior to embolization, all patients had a diagnostic hysteroscopy to exclude intracavitary pathology. Pelvic MRI was performed in all women before treatment.
Emboliization procedure

With a 4 French braided Cobra (C2) catheter the left uterine artery (UA) was selectively catheterized. A coaxial microcatheter was then positioned in the horizontal part of the UA, preferably distally to the cervicovaginal branches. The embolization material consisted of calibrated microspheres (Embogold or Embosphere, Biosphere Medical Roissy, France) or non spherical polyvinyl alcohol (PVA) particles (Contour, Boston Scientific, Freemont CA) (7,8). The aim of embolization was to occlude the branches to the fibroid without complete occlusion of the uterine artery. After embolization of the left UA, the catheter was guided into the right UA by means of the Waltman loop manoeuvre and the right UA was embolized (9,10). In women who wanted to conceive, both femoral arteries were punctured and embolization was performed by two radiologists simultaneously in order to limit radiation exposure of the gonads (11). The patients were scheduled for one night of clinical observation. Pain was controlled by administering 10 mg Morphine intramuscularly, Voltaren 100 mg supp and when necessary Paracetamol or a PCA (patient controlled analgesia) pump. Nausea was treated intravenously with Lithican or Zofran.

Questionnaire

In January 2003, all women embolized between August 1998 and December 2002 received a questionnaire. The questions were aimed at changes in bleeding (menorrhagia and metrorrhagia), pain (dysmenorrhoea, dyspareunia, backpain, pain in the legs and pelvic pain) and bulk-related symptoms (size of abdomen, constipation, urinary frequency and suprapubic pressure). Symptoms after UAE were scored as disappeared, improved, unchanged or worsened. In addition, adverse events were noted such as vaginal dryness and discharge, menopausal complaints or fibroid expulsion. Patient satisfaction after UAE was assessed by the following questions: how would you score your quality of life (improved, unchanged or worse)? Would you opt for the same treatment in retrospect? Would you recommend UAE to a friend?

The patients were also asked whether hysterectomy or additional embolization was performed after the initial embolization. In these cases the women were asked to score their symptoms and satisfaction prior to these additional treatments.
Comparison of embolic agents
Patient satisfaction of women embolized with non spherical PVA particles was compared to women embolized with calibrated microspheres. Statistical analysis was performed using the Chi-square test. P-values <0.05 were considered statistically significant.

Results

Between August 1998 and December 2002, 135 consecutive patients with symptomatic uterine fibroids were embolized. Mean age was 42.9 years, median 44 years, range 25-53 years. (Fig. 1)

![Figure 1. Patient's age (average 43 years; range: 25-52 year)](image-url)
The questionnaire was returned by 110 of 135 women (81%). Mean time interval between embolization and return of the questionnaire was 15.8 months (median 14 months, range 2 to 52 months). Table 1 shows the symptoms of the 110 women before and median 14 months after treatment. In 3 women additional embolization was needed and 6 women had undergone hysterectomy because of insufficient results after initial UAE. One woman underwent hysterectomy after second UAE because of suspected malignancy on follow-up MRI. Pathological examination revealed a fibroid.

Table 1. Symptoms before and at a median follow-up of 14 months after UAE

|                         | before embolization | after embolization | |
|-------------------------|---------------------|--------------------|---|
|                         | disappeared | improved | unchanged | worsened | new symptoms |
| **Bleeding**             |            |            |            |           |             |
| menorrhagia/metrorrhagia| 98  28  29% | 49  50%     | 13  13%    | 8  10%    | 0  0%        |
| anaemia                 | 46  27  59% | 13  28%     | 5  11%     | 1  2%     | 0  0%        |
| **Pain**                |            |            |            |           |             |
| dysmenorrhoea           | 55  15  27% | 24  43%     | 12  22%    | 9  16%    | 5  5%        |
| dyspareunia             | 24  12  50% | 8  33%      | 4  17%     | 2  8%     | 2  2%        |
| back pain               | 45  12  27% | 20  44%     | 9  20%     | 4  9%     | 0  0%        |
| pain in legs            | 31  11  35% | 7  23%      | 12  39%    | 1  3%     | 0  0%        |
| pelvic pain             | 36  11  31% | 17  47%     | 10  28%    | 5  14%    | 7  6%        |
| **Bulk related**        |            |            |            |           |             |
| size of abdomen         | 66  14  21% | 30  45%     | 18  27%    | 4  7%     | 0  0%        |
| constipation            | 17  1    6%  | 11  65%     | 5  30%     | 0  0%     | 0  0%        |
| pollakisuria            | 48  15  31% | 19  40%     | 14  29%    | 2  4%     | 2  2%        |
| supra pubic pressure    | 58  20  34% | 25  43%     | 11  19%    | 4  7%     | 2  2%        |
| **Various**             |            |            |            |           |             |
| vaginal dryness         | 7   1    14% | 3  43%      | 1  14%     | 2  28%    | 0  0%        |
| vaginal discharge       | 28  4    14% | 12  43%     | 11  40%    | 3  11%    | 2  2%        |

Table 1. Symptoms of the 110 patients before and at a median follow-up of 14 months after UAE
Menorrhagia and metrorrhagia disappeared in 29% or improved in 50% of the women respectively, while symptoms of anaemia disappeared in 59% and improved in 28%. A substantial improvement or complete disappearance was seen for all kinds of pain symptoms. However, there was a mediocre response following embolization with regard to pain in the legs. Only 58% of the 31 women who had this complaint before embolization stated that this symptom had disappeared (35%) or improved (23%). Bulk-related problems disappeared to the same degree as bleeding and pain symptoms. In various other complaints the response was less favourable. Some patients experienced new (mild) symptoms not present before UAE.

Of the 110 responders, 86 (78%) were satisfied after UAE. Ten women (9%) were satisfied nor unsatisfied (unchanged) and 14 women (13%) were unsatisfied. Eighty of the 110 women (72%) would opt for the same treatment and 92 (83%) would recommend this treatment to a friend. These results included the 10 women who had additional therapy after initial UAE and were unsatisfied with the initial result.

Temporary amenorrhoea was reported by 19 (17%) women and persisted for up to 6 months following embolization. Permanent amenorrhea was reported by 3 women (47, 49 and 50 years of age). None of the 110 patients experienced vaginal dryness after embolization. Vaginal discharge was reported as an adverse event by two patients. Spontaneous vaginal expulsion of a fibroid occurred in 4 women (3.6%) without further complications.

In 107 patients (97%) bilateral embolization was technically successful; in one patient it was not possible to embolize both uterine arteries from a unilateral approach. The proportion of the 71 women embolized with calibrated microspheres that were satisfied (84.5%) was higher than that of 39 women embolized with non spherical PVA (66.6%) but this difference was not statistically significant (P=0.053).
Discussion

The purpose of the embolization was treatment of the symptoms caused by the uterine fibroids by means of devascularization of all fibroids. Devascularization is achieved by occlusion of the arterial branches to the fibroids with embolic agent. Devascularization and the subsequent decrease in volume of the uterus and fibroid results in elimination or improvement of the patient’s symptoms.

In this retrospective study with mid-term clinical follow-up, UAE was a safe and effective treatment for symptomatic uterine fibroids. The uterus was preserved in 128 of 135 women (95%). At a median follow-up of 14 months, improvement of clinical symptoms was apparent in the vast majority of women and patient satisfaction was high. This is in concordance with previous studies (3-5,12,13). Of 110 women, 14 women (13%) were unsatisfied and 10 had additional therapy. Seven of the 135 embolized patients have had a hysterectomy after UAE; this proportion is similar to that reported in other studies (14).

Inadequate devascularization may occur when other arterial branches feed the fibroid such as anastomoses from the ovarian artery (12,15). Incomplete devascularization may also occur when it is not possible to embolize both uterine arteries. In our study this happened in three patients, nevertheless all were satisfied with their clinical outcome.

Adverse events were limited. Temporary amenorrhea following UAE was reported in 17% and permanent amenorrhea in 3%. Temporary or permanent amenorrhea as a result of ovarian infarction or ischemia may occur when part of the embolization material reaches the blood supply to the ovaries via shunts from the uterine artery. This occurs predominantly in women over the age of 45 where blood supply to the ovary is marginal and ovaries appear to be more vulnerable (16,17). All 3 women in our series developing permanent amenorrhea were over 45 years of age. If shunts to the ovary are identified, we upsize to a larger particle or microsphere unlikely to pass through these small utero-ovarian shunts (9,13).
Vaginal dryness was not reported by any of the responders in our study. Vaginal dryness due to atrophy of the vaginal mucosa may occur when the embolization material obstructs the vaginal branches of the UA. Vaginal discharge was only reported by 2 women as a new symptom after UAE. It has been postulated that vaginal discharge may be associated with submucosal location of the fibroids and may precede spontaneous vaginal expulsion of a fibroid (18); Fibroid expulsion or myoma nascens is a well known fact from literature (19); in our study spontaneous vaginal expulsion of a fibroid occurred in 4 (4%) patients without further complications.

There was a tendency for higher patient satisfaction with the use of calibrated microspheres compared to non spherical PVA as an embolic agent. This difference however was not statistically significant. In a previous study comparing both embolic agents, no significant difference was found either (20).

Of the 135 embolized women 110 have returned the questionnaire. Of the 25 patients who did not return the written questionnaire, 21 had a follow-up MRI. Each MRI was combined with a consultation with an interventional radiologist who collected the data. Thus, some information was available. These 21 women had no complications after UAE and none underwent a hysterectomy. These women were generally positive about UAE: 16 of 21 women with MRI follow-up would opt for the same treatment again.

The limitation of this retrospective study is the questionnaire we used; it was home made, based on the experience we built up over time with this category of patients. Disease-specific Quality of Life questionnaires were unsuitable, because these have to be filled in prospectively several times so as to be able to assess experiences over a period of time, whereas our study consisted of a once-only retrospective questionnaire. Various authors have postulated that UAE is no longer experimental; it is an effective therapy for fibroids and has to be considered in every patient suffering from fibroids (21,22). Our study also shows that UAE in women with symptomatic uterine fibroids leads to improvement of symptoms and patient satisfaction is good in the vast majority after a median follow-up period of 14 months.
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LONG-TERM OUTCOME OF
UTERINE ARTERY EMBOLIZATION
FOR SYMPTOMATIC UTERINE
LEIOMYOMAS
Abstract

Purpose
To evaluate long-term outcomes and factors associated with treatment failure after uterine artery embolization (UAE) in women with symptomatic uterine leiomyomas.

Materials and Methods
One hundred consecutive women treated with UAE for symptomatic uterine leiomyomas participated. Clinical outcome data (i.e. changes in symptoms, menstrual status, and subsequent therapies) and satisfaction data were collected. Treatment failure was defined by subsequent major surgery (i.e. hysterectomy or myomectomy), a second embolization, or a lack of symptom improvement at the patient's final follow-up interval. Possible predictors of failure were age, clinical baseline characteristics (i.e. bleeding, pain, and bulk), and imaging results (i.e. percent volume reduction of the dominant tumor). Cox proportional-hazards analysis was used to determine factors associated with failure.

Results
Follow-up was available in 93 women (median follow-up, 54 months; range, 45-87 y). Continued symptom relief was observed in 72% of patients (n=67). Among the 26 women with treatment failure (28%), 11 (42%) underwent hysterectomy, 4 (15%) myomectomy, and 8 (31%) repeat embolization. Three (12%) reported no improvement. In women without any additional surgery (n=70), heavy menstrual bleeding, pain, and bulk-related symptoms improved in 97%, 93%, and 92%. Ninety percent of all women (n=93) were satisfied or very satisfied at final follow-up. Predictors of failure were a lack of improvement in bleeding (hazard ratio (HR), 9.0; 95% CI, 3.1-26.3; P<0.001) or pain (HR, 7.4; 95% CI, 2.2-24.4; P< 0.001) at 1 year after UAE and the percent reduction in dominant tumor volume (HR, 0.97; 95% CI, 0.95-0.99; P=0.007).

Conclusion
UAE in women with symptomatic leiomyomas leads to long-term symptom improvement. Predictors of failure were a lack of improvement in bleeding or pain at 1 year and the percent reduction in dominant tumor volume.
Introduction

Uterine leiomyomas are common benign tumors in women of childbearing age. Symptomatic uterine leiomyomas can be treated by medical treatment or surgery (1). For several reasons (2), an increasing number of women want to preserve their uterus, leading to the development of uterus sparing therapies such as uterine artery embolization (UAE), myomectomy, and high-intensity focused ultrasound treatment. UAE was introduced as an alternative treatment to surgery for women with symptomatic leiomyomas (3). The employment of this treatment has increased rapidly. UAE has been recognized as an effective alternative to hysterectomy and myomectomy (4). Several published studies showed favorable clinical outcomes and satisfaction at as long as 1 year after embolization (5–10). However, these results do not guarantee similar results later on, and little has been reported regarding long-term outcomes after UAE (11-13). The aim of the present study was to investigate long-term clinical results (mean follow-up, 54 months; median, 54 months; range, 42-87 months), the incidence of additional therapies, and long-term patient satisfaction. An additional aim was to assess factors influencing the clinical outcome and patient satisfaction after UAE.

Materials and Methods

Women participating in this study were the first 100 consecutive patients treated between August 1998 and July 2002 with UAE for symptomatic leiomyomas at a single institution. This study was approved by the local medical ethical committee as required by law. Informed consent was obtained from all participants.

Inclusion and Exclusion Criteria
The study included women with symptomatic uterine leiomyomas, an indication for hysterectomy, and a minimum follow-up period of 3.5 years. This included women who, for personal reasons such as a possible desire to conceive in the future, did not want to undergo hysterectomy. The symptoms were divided into three groups: bleeding problems (i.e. menorrhagia with or without anemia or metrorrhagia), pain (i.e. dysmenorrhoea, dyspareunia, and pelvic pain), and bulk-related problems (i.e. subjective size of an enlarged abdomen, pressure on bladder or rectum with symptoms
of urinary frequency and constipation). All women underwent one or more of the following treatments without sufficient clinical results: iron supplementation, various hormonal treatments (54%), gonadotropin-releasing hormone analogue treatment, levonorgestrel-containing intra uterine device use, use of hemostatic agent (i.e. tranexamic acid), analgesic agent use, myomectomy, or myolysis (i.e. coagulation of blood supply to the uterine tumor). Postmenopausal or pregnant women were excluded, as were women with suspected or confirmed gynecologic malignancy, avascular calcified leiomyomas, any gynecologic infection, pure adenomyosis (without any leiomyomas), or thin-stemmed pedunculated leiomyomas with a stalk diameter smaller than one third of the tumor diameter. Tumor or uterus size (or volume) was not a factor in any exclusion criterion. Before UAE, standard gynecologic assessment (including diagnostic hysteroscopy to exclude intracavitary pathologic processes) was performed. In addition, pelvic magnetic resonance (MR) imaging was done at baseline and at 3-, 6-, and 12-month follow-up. MR imaging was performed to confirm the diagnosis of uterine leiomyomas, measure the size of the uterus, and determine the size and location of the dominant leiomyoma. Adenomyosis was identified if present. The number of leiomyomas was estimated and divided into 4 categories: 1, 2, 3 or at least 4 tumors. Tumor and uterine volumes were calculated according to the formula for a prolate ellipse (length x width x diameter x 0.5233) as described by Orsini et al (14). In December 2005, all women were asked to complete the same questionnaire as in previous stages of the study. Patients were asked to indicate whether they were experiencing bleeding, pain, or bulk-related symptoms. In comparing answers to the questionnaire between time points, we noted whether symptoms changed, and this was scored as improved or not improved. Adverse events such as vaginal infections and/or dryness, leiomyoma expulsion, and menopausal symptoms were recorded. At each time point, patient satisfaction results were classified as very satisfied, satisfied, or not satisfied. Women with a potential desire to conceive in the future were asked if they had become pregnant or tried to become pregnant after UAE. An inventory was made of all subsequent gynecologic therapies after UAE: any medical therapies, surgical interventions (i.e. hysterectomy, myomectomy, hysteroscopic resection of leiomyomas, or diagnostic hysteroscopy and curettage) or additional UAE procedure; and the exact moment of their occurrence. Major interventions were defined as hysterectomy, myomectomy, or repeat embolization according to the classification by Spies et al (11).
Cases were considered failures when an additional major intervention was needed or no improvement was seen at final follow-up.

**Embolization Procedure**

Embolization was started after selective catheterization of the left uterine artery, guiding of the catheter into the right uterine artery by means of the Waltman loop manoeuvre (15), and embolization of the right side. The intention was to carry out bilateral embolization in all women. When spasm in the uterine artery occurred, it was treated medically with tolazoline or nitroglycerin. In women who wanted to become pregnant, both femoral arteries were punctured and embolization was performed by two radiologists simultaneously to limit radiation exposure of the ovaries. The embolization material consisted of nonspherical polyvinyl alcohol (PVA) particles (Contour; Boston Scientific/Target Therapeutics, Fremont, California) 355-710 µm in size or calibrated tris-acryl gelatin microspheres (CTGM’s; Embosphere and Embogold, Biosphere Medical, Roissy, France) 500-900 µm in size. We switched completely from PVA particles to CTGM’s after the first 45 treatments because CTGM’s were easier to use in targeted embolization of the peritumoral plexus with no intracatheter aggregation and blockage. With PVA particles, the aim was to achieve a proper angiographic embolization endpoint, i.e. proximal total occlusion of both uterine arteries. When using CTGM’s, the angiographic embolization endpoint was defined as complete occlusion of branches to the peritumoral plexus and sluggish flow in the ascending segment of the uterine artery, leaving the main uterine artery, cervicovaginal branches, and utero-ovarian anastomoses patent. The choice of embolic agent used was influenced by factors such as operator preference of a new technique selected at the time and was independent of patient or tumor characteristics. Women stayed hospitalized for one night for clinical observation. Before the procedure, antibiotics (2 g cefazolin) were administered intravenously. Pain was controlled by administering 10 mg morphine intramuscularly and a 100 mg suppository of a nonsteroidal anti-inflammatory drug or a patient-controlled analgesia pump. Nausea was treated with 4 mg ondansetron.
**Statistical Methods**

Univariate analyses were used to determine the distribution of each baseline and outcome measure. Patients were stratified into clusters according to all possible combinations of symptoms (i.e. bleeding, pain, and bulk). Subsequently, analyses of variance were performed to examine the relationship between (i) these clusters and the number of additional therapies and (ii) the clusters and clinical improvement. We considered patients to have shown clinical improvement when all leiomyoma-related symptoms within the cluster had improved after UAE. To determine the relationship between major interventions (i.e. hysterectomy, myomectomy, or repeat embolization) and baseline characteristics, clinical results, and imaging results during the first year after UAE, Cox proportional-hazards regression analysis was used. The variables included were age, indication for UAE (i.e. bleeding symptoms, pain, or bulk-related symptoms), therapies before UAE, number and localization of leiomyomas, presence of apparent adenomyosis, embolization material used (i.e. nonspherical or spherical particles), uni- or bilateral procedure, baseline volumes of the uterus and dominant leiomyoma, percent reduction in volume at 3 and 6 months after UAE, symptoms at 3 and 6 month follow-up, and hormonal therapies started after UAE. Survival time was defined in months from UAE until censorship. Cox proportional-hazards regression analysis was also employed to determine the relationship between long-term failure (i.e. major intervention or no improvement at final follow-up) and baseline characteristics and imaging results. In addition to the variables mentioned earlier, percentage volume reduction and symptoms at 12 months after UAE were included. Women who had a major intervention in the first 12 months after UAE were excluded from this analysis. Cox proportional-hazards regression was performed for all cases of treatment failure (i.e. major intervention or no improvement at final follow-up) during the whole follow-up period. The same covariates as mentioned earlier were used in this analysis. In addition, Cox proportional-hazards regression was used to examine the association between dissatisfaction with UAE over the whole follow-up period and covariates. Covariates were baseline characteristics; clinical and imaging results at 3, 6, and 12 months; and any subsequent interventions. Data are presented as medians with ranges or means with SD’s, and Cox proportional-hazards regression results are presented as hazard ratios (HR’s), 95% CI’s, and P-values. P-values less than .05 were considered statistically significant. Data were analyzed with SPSS software (version 12.0; SPSS, Chicago, IL).
Results

Of the 100 women enrolled in the study, follow-up data were obtained at 3 and 6 months in 92 women, at 12 months in 89 women, and at final follow-up in 93 women. The median final follow-up time after UAE was 54 months (range 42-87 months). Two patients died during follow-up: one of pulmonary carcinoma and one of pre-existing chronic obstructive pulmonary disease. Five women could not be traced. The mean age of the women at the time of UAE was 43 years (range 25-53 y). Forty percent of women (n=40) did not have children and 19% had never been pregnant. Ninety-four women were white, five were black, and one was Asian. Additional general characteristics are listed in Table 1.

| Characteristic                  | Incidence (%) |
|--------------------------------|---------------|
| Indication for UAE              |               |
| Menorrhagia/anemia              | 94            |
| Pain                            | 57            |
| Bulk-related symptoms           | 54            |
| Number of leiomyomas            |               |
| 1                               | 33            |
| 2                               | 12            |
| 3                               | 5             |
| ≥4                              | 50            |
| Location of dominant leiomyoma  |               |
| Intramural                      | 78            |
| Submucosal                      | 22            |
| Subserosal                      | 10            |
| Pedunculated                    | 4             |

Table 1. General Patient Characteristics (n=100)
| Results       | 3 Months | 6 Months | 12 Months | Median 54 Months |
|--------------|----------|----------|-----------|-----------------|
| Missing data | 8        | 8        | 11 (1†)   | 7 (2†)          |
| Major intervention | 3/92 (3) | 7/92 (8) | 10/89 (11) | 23/93 (25)      |
| Hysterectomy | 3/92 (3) | 3/92 (3) | 4/89 (4)  | 11/93 (12)      |
| Myomectomy   | 0/92 (0) | 2/92 (2) | 3/89 (3)  | 4/93 (4)        |
| Repeat UAE   | 0/92 (0) | 2/92 (2) | 3/89 (3)  | 8/93 (9)        |

**Bleeding‡**

| Improved       | 72/83 (87) | 72/80 (90) | 62/73 (85) | 64/66 (97) |
| Not improved   | 11/83 (13) | 8/80 (10)  | 11/73 (15) | 2/66 (3)   |

**Pain‡**

| Improved       | 46/50 (92) | 46/48 (96) | 40/45 (89) | 38/41 (93) |
| Not improved   | 4/50 (8)   | 2/48 (4)   | 5/45 (11)  | 3/41 (7)   |

**Bulk‡**

| Improved       | 46/50 (92) | 46/51 (90) | 38/45 (84) | 35/38 (92) |
| Not improved   | 4/50 (8)   | 5/51 (10)  | 7/45 (16)  | 3/38 (8)   |

**Satisfaction‡**

| Very satisfied | 24/89 (27) | 39/86 (45) | 45/79 (57) | 51/70 (73) |
| Satisfied      | 55/89 (62) | 36/86 (42) | 27/79 (34) | 18/70 (26) |
| Not satisfied  | 10/89 (11) | 11/86 (13) | 7/79 (9)   | 1/70 (1)   |

**Table 2. Clinical Results and Major Interventions**

Values in parentheses are percentages unless otherwise specified.

* Cumulative major interventions comprising the three rows below.
† Number of patients who died before the follow-up interval.
‡ Changes in symptoms and satisfaction are displayed for women who were not missing at that interval and did not undergo a major intervention until then.
The mean baseline uterine volume obtained by MR imaging was 510 ml (median, 403 ml; range 54-1,750 ml). The mean dominant leiomyoma volume was 170 ml (median 130 ml; range 2-1,123 ml). Five women had apparent adenomyosis accompanying the leiomyomas. With regard to unsuccessful types of treatment before UAE, hormones were the most frequent form of treatment (54%), of which 42% constituted oral contraceptives, 5% hormone replacement therapy, 13% progestativa, and 1% danazol. In addition, gonadotropin releasing hormone analogues were used by 14% of women and a levonorgestrel-containing intrauterine device was used by 4%. Iron supplements were used by 44% of the women, analgesics by 6%, and laparoscopic myomectomy, hysteroscopic myomectomy, and myolysis were performed in 3%, 8%, and 1% of women, respectively. UAE was performed bilaterally in 97 women and unilaterally in 3 women as a result of spasm (n=2) or aplasia (n=1) of 1 uterine artery. After the first year, 11% of women (10 of 89) needed a major intervention and data from 11 women were missing (Table 2). Of the remaining 79 women, bleeding improved in 85% (62 of 73), pain in 89% (40 of 45), and bulk-related symptoms in 84% (38 of 45). Regarding satisfaction, 91% of women (72 of 79) were very satisfied or satisfied. At the final follow-up, the incidence of major interventions increased to 25% (23 of 93) and data from seven women were missing. Of these remaining 70 women, bleeding improved in 97% (64 of 66), pain in 93% (38 of 41), and bulk-related symptoms in 92% (35 of 38). Three women reported no improvement at all. The satisfaction score was 99% (69 of 70 very satisfied or satisfied). With all women included (n=93), the satisfaction was 90% (84 of 93) after a median of 54 months of follow-up. Subsequently, women were stratified into all possible combinations of the 3 symptoms before UAE. This resulted in 7 clusters, of which 3 were very small. No woman reported pain only, one woman had pain and bulk-related symptoms, and 5 women had only bulk-related symptoms (Table 3). There were no differences among symptom clusters with regard to the number of additional therapies or improvement of symptoms after UAE (P=0.71; Table 3).

Of the 23 women with a major intervention, 11 underwent hysterectomy, 4 myomectomy, and 8 repeat UAE. Of these 23 women, 19 exhibited insufficient tumor infarction on contrast agent-enhanced MR imaging at 3 months. Insufficient infarction was a result of unilateral embolization in 1 woman, spasm in 5 women, and insufficient embolization (i.e. no proper angiographic embolization endpoint) in the
| Symptom | No. of pts | Lost to follow-up | Pts with clinical improvement* | Hysterectomy | Myomectomy | Repeat UAE | Median (range) Follow-up months |
|---------|------------|-------------------|--------------------------------|---------------|-------------|------------|-------------------------------|
| bleeding | 32 | 3 | 21/22(95) | 3 | 1 | 3 | 48.3 (41.8-80.0) |
| pain | 0 | - | - | - | - | - | - |
| bulk | 5 | 0 | 3/3(100) | 2 | 0 | 0 | 56.1 (42.7-87.1) |
| Bleeding and pain | 19 | 1 | 12/13(93) | 2 | 1 | 2 | 58.1 (42.5-80.0) |
| Pain and bulk | 1 | 0 | 1/1(100) | 0 | 0 | 0 | 52.0 (52.0-52.0) |
| Bleeding and bulk | 12 | 1 | 6/9(67) | 1 | 1 | 0 | 56.5 (44.4-66.5) |
| Bleeding, pain & bulk | 31 | 2 | 20/22(90) | 3 | 1 | 3 | 48.3 (41.8-80.0) |

**Table 3.** Symptom Clusters before UAE and Clinical Improvement
A patient is improved when all symptoms in a particular cluster have improved. Values in parentheses are percentages

| Symptom | Early failure 0-12 months after UAE | Late failure 12 months after UAE | Overall failure UAE through final follow-up |
|---------|-------------------------------------|---------------------------------|---------------------------------------------|
| **After 3 months** | | | |
| Bleeding | 8.2(2.0-33.6) P=.003 | 5.5(1.2-25.5) P=.030 | 7.6(2.8-2.5) P<.001 |
| Pain | NS | NS | 3.5(1.2-10.6) P=.025 |
| Bulk | NS | 7.5(1.6-34.1) P=.010 | NS |
| **After 6 months** | | | |
| Bleeding | 25.6(4.9-133) P<.001 | NS | 7.2(2.7-19.3) p<.001 |
| Pain | NS | 7.3(1.6-34.1) P=.010 | 5.6(1.6-1.5) P=.007 |
| Bulk | NS | NS | NS |
| **After 12 months** | | | |
| Bleeding | 11.4(3.5-37.4) P<.001 | NS | 9.0(3.1-26.3) P<.001 |
| Pain | 12.6(3.5-45.7) P<.001 | 7.4(2.2-24.4) P<.001 |
| Bulk | 4.2(1.2-15.3) P=.029 | NS |

**Table 4.** Symptoms after UAE as Predictors for Future Failure
remaining 13 women. Of the 8 women who underwent a second embolization, none exhibited vasospasm during the first UAE procedure. In addition, 2 cases of necrotic leiomyoma (with fever) and new symptoms resulting from new leiomyomas in 2 women necessitated major intervention. The median time between UAE and major intervention was 18 months (range 2-49 months). Eight women underwent repeat UAE: 7 had complete symptom relief after the second procedure and 1 had complete symptom relief after the third procedure. To determine a UAE learning curve, outcomes in the first 50 women were compared with the second 50 women. No difference was found between the groups. Thirty-four of 93 women (37%) started using hormonal therapy. Indications were contraception (n=14), menopausal or postmenopausal symptoms (n=7), endometriosis (n=3), and menstrual discomfort (n=3). In 7 women, recurrent symptoms were the reason to start hormonal therapy. Five needed subsequent major intervention.

The median uterine and dominant leiomyoma volumes measured at 3, 6 and 12-month follow-up are displayed in the Figure.

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**Figure.** Median volumes measured at 0, 3, 6 and 12 months after UAE.
Median volume reductions of the dominant leiomyomas were 44%, 53%, and 61%, whereas uterine volume reductions were 31%, 40%, and 44%, respectively at 3, 6 and 12 months. Transient amenorrhea after UAE was observed in 17% of women (16 of 93). Leiomyoma expulsion was reported in 12% (n=11). Twenty-nine women (33%) had become postmenopausal. The mean ages of this group of women were 48 years (SD, 3.0 y) at the time of embolization and 50 years (SD, 3.3 y) at their first report of permanent amenorrhea. The mean interval from UAE until permanent amenorrhea was 23 months (median 24 months; range 0- 46 months). Transient vaginal discharge was reported in 17% of women (n=16). Eight percent of women reported vaginal infections, mainly during the first months after UAE. Vaginal dryness was noted in 15% (n=14). However, this started mostly after the onset of permanent amenorrhea and not directly after UAE. Before embolization, 16% of women (n=16; mean age 37.6 years) had a possible desire to conceive after UAE and 10% (n=10) were actively seeking to become pregnant (mean age 36.5 years). However, after UAE only 4 women actually attempted to become pregnant. One woman became pregnant twice and delivered 2 full-term children. No peripartum complications were noted. One woman was 9 weeks pregnant at the last follow-up. The other 2 women did not become pregnant. A lack of improvement in bleeding symptoms at 3 and 6 month follow-up was a significant predictor of a major intervention during the first year (Table 4). None of the other covariates assessed was of significant influence on early failure.

Sixteen of 89 women (18%) had late failure, i.e. a major intervention after the first year after UAE or a lack of improvement at final follow-up. Bleeding symptoms and bulk-related symptoms that not improved at 3 months were significant predictors of failure in the future, as was a lack of improvement of pain at 6 months (Table 4). A lack of improvement in bleeding, pain or bulk-related symptoms at 12-month follow-up were all predictors of future failure. The percent reduction of dominant leiomyoma volume at 12 months was related to long-term failure. For each percent increase in volume reduction, the chance for future failure decreased by a factor of 0.97 (i.e. HR of 0.97; 95% CI 0.95-0.99; P=0.007). In addition, the percent reduction of uterine volume was significantly associated with failure (HR of 0.98; 95% CI 0.96-1.0; P=0.049), but after adjusting for percent reduction of dominant leiomyoma volume, this association was no longer significant (P=0.54). All other covariates assessed were of no significant influence.
Subsequently, predictors of overall failure (i.e. major interventions or lack of improvement at final follow-up) over the total follow-up period were examined. Twenty-six cases met the criteria for treatment failure. No improvement in bleeding symptoms and pain were significant predictors of future failure at 3, 6, and 12 months after UAE (Table 4). The percentage volume reduction of the dominant leiomyoma at 12 months was significantly associated with future failure (HR 0.97; 95% CI 0.95-0.99; P=0.008). Less volume reduction of the leiomyoma was associated with an increased chance of failure. We did not find age at the time of UAE to be related to future failure (P=0.56).

No significant relation was found between the baseline volumes of the uterus and dominant tumor and future failure (P=0.70 and P=0.86, respectively). All other covariates assessed were not of significant influence. All women were included in the analysis of satisfaction with UAE. At the final follow-up, 9 of 93 women (10%) were not satisfied. The association between dissatisfaction and baseline characteristics, clinical outcome, and imaging results were determined. A subserosal localization of the dominant leiomyoma was significantly associated with dissatisfaction at final follow-up (HR 5.5; 95% CI 1.4-21.5; P=0.013). A lack of improvement of bulk-related symptoms at 3 and 12 months after UAE was also significantly associated with dissatisfaction (HR 12.0; 95% CI 1.2-118.1; P=0.033; respectively; HR 14.4; 95% CI, 2.0-103.5; P=0.008) at the final follow-up. Women who had a major intervention were almost 21 times more likely to be dissatisfied at final follow-up than women who did not have a major intervention (HR 20.6; 95% CI 2.6-165; P=0.004). Regarding major interventions, hysterectomy was significantly associated with dissatisfaction at the final follow-up (HR 41.8; 95% CI 5.2-338.4; P< 0.001). For myomectomy and repeat UAE, no significant relationship was found. When a case was defined as a failure at the final follow-up, this was also associated with patient dissatisfaction with treatment (HR 15.6; 95% CI 1.9-126.1; P=0.010). No other characteristics predicted dissatisfaction at final follow-up.
Discussion

The aim of the present study was to investigate long-term clinical results, rate of additional therapies, and long-term patient satisfaction, and to assess factors influencing clinical outcomes and patient satisfaction after UAE. We found continued symptom relief in 72% of the women treated with UAE, and 90% reported to be satisfied or very satisfied after a median follow-up of 54 months. Although 25% of the women underwent a major intervention, only 12% needed a hysterectomy. Our findings are comparable to the results of Spies et al (11), who found continued symptom relief in 73%, a major intervention rate of 20%, and a hysterectomy rate of 14%. Katsumori et al (13) reported a symptom control rate of 89.5% at 5 years after UAE with gelatin sponge particles. Walker and Barton-Smith (12) reported high symptom control rates and a 16% incidence of subsequent interventions after UAE. In contrast to existing studies, we looked at seven symptom clusters, i.e. possible combinations of symptoms presented by the women before UAE. We showed that 3 symptom clusters are uncommon: pain only, bulk only, and the combination of the two. The majority of patients reported more than one symptom, mostly in combination with bleeding. With regard to long-term outcomes in the different clusters, we found no significant difference in improvement. Moreover, in our study, the symptom clusters did not result in differences concerning additional therapies. In our study, the number of women who started to use hormonal therapy (for various reasons) after UAE was high. The literature about the effects of hormonal therapy in women with leiomyomas is not conclusive (16,17).

In our analysis, no significant relation was found between the use of hormones after UAE and the risk of subsequent major interventions. Several factors associated with major intervention or failure after UAE were identified in this study, i.e. menorrhagia or pain after 12 months. After a mean observation period of 13 months after UAE, Huang et al (18) found persistent menorrhagia and persistent abdominal pain to be present in 59% and 23% of women who required additional surgery, respectively. Spies et al (11) showed that long-term failure was more likely in women who had not experienced an improvement at 1-year follow-up; however, they did not stratify this for different symptomatologies. The percentage volume reduction of the dominant leiomyoma at 12 months after UAE was a predictor for long-term failure and failure in the total follow-up
Spies et al (11) reported also that decrease in volume reduction of the dominant tumor was associated with failure. Investigators have been concerned about the effect of uterine volumes on clinical outcome. Some reports failed to show any correlation (19,20), whereas others demonstrated favorable outcomes after UAE in large uterine volumes (21,22). Kido et al (21) reported remarkable symptom improvement in women with large uterine volumes of diffuse leiomyomatosis. Prollius et al (22) described that large uterine volumes did not decrease the efficacy of UAE, but concluded that, in women with a very large uterus and predominant bulk-related symptoms, alternative treatment options should be explored because, after UAE, these women are still left with a large mass. Marret et al (23) defined two predictive factors for leiomyoma recurrence after UAE at a median of 30 months of follow-up: the number of tumors and the size of the dominant tumor. Spies et al (11) also reported long-term failure to be more likely in those with baseline dominant tumor volumes greater than the median measurement.

In our study, we did not find any baseline characteristic of significant influence. Size and number of leiomyomas are of lesser importance to clinical outcome. Because no baseline predictors or conditions associated with failure were found in this study, it remains difficult to select women with the best chances for a successful outcome beforehand. However, we did find more dissatisfaction in women with a subserosal localization of the dominant tumor. Although not statistically significant, women with bleeding and bulk-related symptoms had less improvement after UAE compared with the other clusters in our study. It might be that, when the group of women in this symptom cluster increases, the difference will be statistically significant. Therefore, gynecologists have an important role in pre- and postprocedural counseling and instituting additional treatment when necessary. Interventional radiologists are necessary in counseling about and performing this specialized procedure. It is of paramount importance to provide women information about the limitations of UAE to avoid unrealistic expectations.

We hypothesize that the infarction percentage of the leiomyoma is the most important factor for a successful clinical outcome of UAE. Pelage et al (24) investigated the clinical differences between women with and without complete infarction of the dominant leiomyoma. Incomplete tumor infarction did not affect outcome immediately,
but the recurrent growth of uninfarcted tissue could lead to symptom recurrence. In our study, the type of embolic agent (nonspherical or spherical particles) did not affect the long-term results, which implies that infarction, rather than the embolic agent used, is of importance. This is in accordance with the results demonstrated by Spies et al (24), who, in a randomized comparative study, reported no substantive differences between outcomes of embolization with PVA particles and CTG’s (25). Comparable with other studies, the patient satisfaction after UAE was high at final follow-up (9,12,26). However, among women who scored their satisfaction as satisfied or very satisfied, some had undergone a major intervention. This was also found by Smith et al (9). An explanation for this contradictory finding could be that women who underwent UAE are a selected population (2,12). Partially as a result of the extensive counselling by the gynecologist and the radiologist in our institution, these women are very motivated to undergo the procedure and are often reluctant to undergo surgery.

A second reason for the high satisfaction rate might be the extra attention during clinical (and scientific) follow-up given to these women who participated in this study. Our current study has some limitations. First, the population of women treated with UAE changed over time. Initially, only small numbers of women were treated with UAE. When more information became available, we started offering UAE to younger women, those who wished to conceive in the future, and those with very large leiomyomas. With regard to UAE in women with symptomatic leiomyomas who wish to conceive, physicians should proceed with caution. Although uncomplicated pregnancies and normal deliveries have been reported after UAE, there is insufficient evidence regarding the safety of the procedure in women seeking to give birth. To date, pregnancy-related outcomes remain understudied (27,28). The current consensus opinion is that myomectomy is the preferred therapy in this subgroup of women with symptomatic uterine leiomyomas who wish to conceive. These women may be offered UAE after failed myomectomy, in cases in which myomectomy may be difficult, or when a surgical option is rejected by the patient (12). The second limitation of our study is that the embolization procedure and its postprocedural management were changed. We switched from nonspherical PVA to spherical CTG’s with a different angiographic embolization endpoint because spherical CTG’s were considered easier to work with, i.e. no occlusion of microcatheters and a more targeted embolization of the uterine leiomyomas. Postprocedural pain management was changed to the primary use of a
patient-controlled analgesia pump. Also, the attitude of the gynecologist toward postprocedural complications became different. Nowadays, we have more knowledge to distinguish symptoms of uterine infection from the more common post embolization syndrome (29). Before performing a hysterectomy, these 2 conditions need to be carefully distinguished because, in the latter, it is justified to remain expectative. These changes of attitude might have had an impact on the clinical outcomes and satisfaction in our study. In the present study, we evaluated the results of 100 women. For some analyses, these women were divided into different groups, with some being small. This leads to very large confidence intervals, as can be seen in the data for predictors of dissatisfaction. Studies with larger numbers of patients are required to allow more definitive conclusions to be drawn. In conclusion, our data show that UAE as treatment for symptomatic uterine leiomyomas leads to long-term improvement of symptoms in the majority of women. Women’s satisfaction is high, even when an additional major intervention is needed. We found no baseline predictors or conditions associated with treatment failure.
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SAFETY AND EFFECTIVENESS OF UTERINE ARTERY EMBOLIZATION IN PATIENTS WITH PEDUNCULATED FIBROIDs
Abstract

Purpose
Pedunculated subserosal fibroids are considered a relative contra-indication for uterine artery embolization (UAE). Decreased blood flow to the pedunculated fibroid may cause septic necrosis and separation from the uterus. The frequency of such complications is unknown. In this retrospective study we assessed complications and outcomes of UAE in women with pedunculated fibroids in a large single center patient cohort.

Materials and Methods
From a database with prospectively collected data of 716 women treated with UAE between 1996 and 2008, 29 women were identified with 31 pedunculated fibroids. MRI prior to embolization and at 3 months was used to calculate stalk diameter change and volume reduction of both pedunculated fibroid and uterus. Two observers assessed overall percentage infarction and infarction of pedunculated fibroid. Complications were recorded and long term clinical follow-up (mean 33 months, range 10-78) was assessed by questionnaire.

Results
Mean uterine and pedunculated fibroid volume reduction was 37% and 33%. Mean stalk diameter reduction was 0.3 cm (95% CI 0.18-0.52 cm) or 13% from initial mean diameter. Stalk enhancement was not affected by UAE.

Mean pedunculated fibroid infarction and mean overall infarction rate were for observer 1; 87% and 92% and for observer 2; 88% and 92% with good inter-observer variability. All women returned the questionnaire and no early or late complications of UAE were reported (0%, 95% CI 0.0-13.9%).

Conclusion
In this small series of pedunculated subserosal fibroids treated with UAE, no complications occurred. Our findings suggest that their treatment with UAE may be safe and effective.
Introduction

Uterine artery embolization (UAE) is increasingly offered as a safe and effective alternative to myomectomy or hysterectomy for symptomatic uterine fibroids (1-9). The presence of pedunculated fibroids is considered a relative contra-indication for UAE (10-12). If a pedunculated fibroid becomes septic after embolization, a hysterectomy is needed: involvement of the bowel due to infection or formation of adhesions may necessitate concomitant partial bowel resection. However, the frequency of such serious complications is unknown. Recent studies of small patient groups indicated that UAE for pedunculated fibroids may be safer than previously thought (13-14). The objective of our study was to retrospectively assess the complications and outcomes of UAE as a treatment for patients with pedunculated fibroids selected from a large single center cohort.

Materials and Methods

Patients
This retrospective study was approved by the Institutional Review Board with a waiver for informed consent. From an institutional database with prospectively collected data of 716 women with symptomatic uterine fibroids treated with UAE between 1996 and 2008, 29 women were identified with 31 pedunculated fibroids, defined as a stalked subserosal fibroid with a stalk diameter of less than half of the fibroid diameter (15). All 29 women were premenopausal with a mean age of 44 years (median 44, range 34-51 years).

Embolization technique
UAE was performed after selective catheterization of the left uterine artery and guiding the catheter into the right uterine artery by means of the Waltman loop manoeuvre. Bilateral embolization via an unilateral approach was performed in all women. The use of a microcatheter was left to the discretion of the physician. In women who desired future pregnancy, embolization was performed on two sides at the same time to limit radiation exposure to the ovaries. Various embolic agents with size of 500–900 microns
were used. The angiographic embolization endpoint was a complete occlusion of branches to the perifibroid plexus, with sluggish flow in the ascending segment of the uterine artery, and leaving the main uterine artery, cervicovaginal branches, and utero-ovarian anastomoses patent.

**Imaging**

All patients had native and contrast enhanced MRI prior to embolization and at 3 months post embolization. From baseline MRI, the diameter of the pedunculated fibroid stalk and the dimensions of the pedunculated fibroid and the uterus were assessed. The diameter change of the stalk and the rates of pedunculated fibroid and uterine volume reduction were assessed by comparison 3 months MRI with baseline. Volume calculation was done by using the formula of a prolate ellipse (length x depth x width x 0.5233). Pedunculated fibroid infarction rate and overall infarction rate (including the pedunculated and all other present fibroids) were assessed by two observers independently on 3 months MRI by visual estimation of decrease in enhancement as compared to baseline MRI. Infarction rates were subsequently classified as 100%, 90-99%, 80-90% and less than 80% (16).

**Outcome and follow-up**

Complications were assessed according to the classification by Goodwin (15) using information collected at the time of the hospital stay or an unanticipated hospital visit, and on an interview and questionnaire at the time of 3 months follow-up MRI. Symptomatic outcome and patient satisfaction were assessed with serial questionnaires as part of the routine follow-up assessment.

In October 2008, at mean 33 months after UAE (range 10-78 months), all 29 women with pedunculated fibroids received a questionnaire about general well being, satisfaction of treatment, residual complaints, additional treatment for the same disorder and the occurrence of late complications needing doctor’s attention or hospital admission.
Data analysis
Complications were calculated as a percentage with 95% CI. Mean volume reduction as a percentage of initial volume of pedunculated fibroid and uterus was assessed. Mean pedunculated fibroid stalk diameter reduction and mean decrease in contrast enhancement was expressed as a percentage. T-test was used for comparison of means. P-values <0.05 were considered significant. Interobserver variability of overall and pedunculated fibroid infarction rates was assessed with κ-statistics. Statistical analysis was performed with MedCalc 10 statistical software (MedCalc, Mariakerke, Belgium).
Results

Mean diameter of the pedunculated fibroid was 7.45 cm (median 7, range 4.5-12.3 cm). Frequency distribution of fibroid size is displayed in Fig. 1.

Mean pedunculated fibroid volume before UAE was 168 cm$^3$ (median 99, range 26-502 cm$^3$) and at 3 months this was 113 cm$^3$ (median 53, range 15-373 cm$^3$). Mean volume reduction of the pedunculated fibroid was 55 cm$^3$ (95% CI 28-82 cm$^3$) or 33% from initial mean volume.

Mean pedunculated fibroid stalk diameter before UAE was 2.6 cm (median 2.5, range 1.6-5.2 cm) and at 3 months this was 2.3 cm (median 2.3, range 1.4-4.1 cm). Mean diameter reduction of the pedunculated fibroid stalk was 0.3 cm (95% CI 0.18-0.52 cm) or 13% from initial mean diameter. All 31 stalks enhanced before UAE and at 3 months 28 stalks still enhanced, in the remaining 3 cases this could not be evaluated (Fig. 2).

Mean uterus volume before UAE was 600 cm$^3$ (median 510, range 47-1808 cm$^3$) and at 3 months this was 377 cm$^3$ (median 352, range 46-1131 cm$^3$). Mean volume reduction of the uterus was 223 cm$^3$ (95% CI 127-317 cm$^3$) or 37% from initial mean volume.

Figure 1. Frequency distribution of maximum diameter in the 31 pedunculated fibroids.
Mean overall infarction rate for observer 1 was 92% and for the pedunculated fibroid only this was 88%. For observer 2 these figures were 92% and 87%. Inter-observer variability for overall infarction rate was good ($\kappa = 0.745$) and for pedunculated fibroid infarction rate this was also good ($\kappa = 0.753$).

All 29 patients responded to the late follow-up questionnaire. There were no early or late complications of UAE (0%, 95% CI 0.0-13.1%). Four patients had a hysterectomy at various intervals after UAE due to persistent complaints with persisting enhancing fibroids. In 3 of these patients the pedunculated fibroid was not dominant and was completely infarcted. In these 3 patients there were no adhesions found at surgery. In one patient who underwent hysterectomy the presumed pedunculated fibroid showed persistent enhancement. However, on pathological examination this revealed to be a leiomyosarcoma. In this patient, extensive adhesions were present during surgery. The remaining 25 women reported improvement or cure of presenting symptoms with a high degree of treatment satisfaction.

**Figure 2.** Contrast enhanced T1 weighted MRI before (A) and 3 months after (B) uterine artery embolization in a 43-year old woman. While the pedunculated fibroid is completely infarcted, vascularization of the stalk is intact (arrow).
Discussion

We found that embolization of symptomatic patients with pedunculated fibroids was safe and effective; after a mean follow-up period of 33 months, no early or late complications had occurred. Although 4 patients needed hysterectomy during the follow-up period, the indication for this additional therapy was not related to the presence of the pedunculated fibroid.

The general conception that pedunculated fibroids are a relative contra-indication for UAE is based on 3 cases as part of 3 early series (12-14). In 2 of these 3 cases, septic necrosis of pedunculated fibroids necessitated emergent hysterectomy. In one woman the septic pedunculated fibroid was closely related to the bowel, and partial bowel resection had to be performed. The third case reported a liquefied change of a pedunculated fibroid leading to an increased size. It must be noted that these early reports did not provide detailed information on important clinical and imaging parameters such as the diameter of the stalk and the size of the pedunculated fibroid before and after embolization. Moreover, the relative frequency of these complications was not accounted for.

Although never documented, there is a general fear that necrosis of the stalk of the pedunculated fibroid may lead to separation of the pedunculated fibroid from the uterus into the abdominal cavity. To clarify this postulation we evaluated the change in vascularization of the stalk by comparing pre and post embolization contrast enhanced MRI's. Remarkably, the enhancement and thus vascularization of the stalk remained unaffected by the embolization in all patients where it could be evaluated, while devascularization and volume reduction of the pedunculated fibroid was significant and in the same magnitude as for the intramural fibroids. Probably, the arterial supply to the stalk is by uterine stroma arteries and not by uterine artery branches to the perifibroid plexus. Following our embolization protocol we did not encounter any over-embolization which might lead to stalk devascularization and infarction. With proper embolization technique, the fear of separation of pedunculated fibroids from the uterus after embolization seems at least premature.
Our finding that embolization of pedunculated fibroids is safe and effective is in concordance with two recent smaller studies with 12 and 16 patients with pedunculated fibroids who underwent UAE (13-14). In both studies, pedunculated fibroid infarction was effective and no complications occurred. Also in these studies, stalk vascularization was not affected by the embolization in all patients were it could be evaluated. A limitation of our study is the limited patient group. However, pedunculated fibroids are rare in the population with symptomatic fibroids that are treated with UAE, in our series just over 4% (29 of 716). A strong point of our study is that patients were well documented with complete and long-term clinical follow-up.

The available data thus far indicate that serious complications of UAE in pedunculated fibroids are probably rare. There is no reason to believe that complication rate of UAE in patients with pedunculated fibroids is higher than in patients with intramural fibroids. Perhaps, the subserosal location of the fibroids may predispose for the formation of intra-abdominal adhesions, but this has not yet been elucidated (17). Although these data are derived from a small number of patients, they suggest that patients with symptomatic fibroids in the presence of a pedunculated subserosal fibroid may still be treated safely with UAE.
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IS AN INTRA UTERINE DEVICE A CONTRA-INDICATION FOR UTERINE ARTERY EMBOLIZATION? A STUDY OF 20 PATIENTS
Abstract

Purpose
The presence of an intra uterine device (IUD) is considered a risk factor for post procedural infection and physicians may prefer to remove the IUD prior to uterine artery embolization (UAE). We retrospectively evaluated the occurrence of infectious complications in 20 women with symptomatic uterine fibroids and an IUD in situ that were treated with UAE.

Methods
Between September 2003 and November 2008, 20 patients with an IUD had UAE for symptomatic uterine fibroids or adenomyosis. At baseline and 3 months after UAE, MR imaging was performed and the Uterine Fibroids Severity and Quality Of Life questionnaire (UFS-QOL) was filled out. In January 2009 all patients responded to a third UFS-QOL questionnaire and an additional questionnaire with emphasis on adverse events and infectious complications.

Results
Mean follow-up interval after UAE was 20.5 months (median 16, range 3-65 months). One patient had a hysterectomy 6 weeks after UAE because of persistent pain. Pathological examination showed ischemia of the uterine stroma without inflammation. Three patients experienced minor adverse events without the need for medical attention: unspecified pain in 2 patients and spontaneous fibroid expulsion in one patient.
In none of the patients infections developed (0%, 95% CI 0-14%). UFS-QOL scores improved from 39 at baseline to 85 at last follow-up.

Conclusion
In this limited group of 20 women with an IUD in situ treated with UAE, no infectious complications developed during hospital stay and follow-up. The presence of an IUD might not be considered as a contra-indication for UAE.
Introduction

Uterine fibroids (leiomyomas) are common benign tumours in women of child-bearing age that may cause bleeding, pain and bulk-related symptoms (1). Uterine artery embolization (UAE) is considered a valuable alternative for medical or surgical treatment of symptomatic uterine fibroids (1-10). Contra-indications for UAE are pregnancy, gynecological malignancy, pelvic inflammatory disease and the presence of spontaneously infarcted fibroids. Although solid evidence is lacking, the presence of an intra uterine device (IUD) is considered a risk factor for post procedural infection and physicians may prefer to remove the IUD before performing UAE. In this paper, we report our experience in 20 such women.

Materials and methods

Patients
This retrospective study was approved by the Institutional Review Board. The need to obtain informed consent was waived. From our institutional database with prospectively collected data of 712 women treated with UAE for symptomatic fibroids and adenomyosis we identified 20 women with an IUD in situ during UAE between September 2003 and November 2008. All 20 women were premenopausal with a mean age of 42.5 years (median age 43, range 35-49 years). Of the 20 women, 15 presented with bleeding, 14 with pain and 12 with bulk-related symptoms. Eighteen women were treated for fibroids and 2 for pure adenomyosis. Before UAE, all patients had a gynecological consultation to confirm that presenting symptoms were caused by uterine fibroids or adenomyosis and not by infection or malignancy.

Imaging
All patients underwent native and contrast enhanced magnetic resonance (MR) imaging before UAE and 3 months thereafter. Volumes of the dominant fibroid and uterus were calculated from MR images by using the formula of a prolate ellipse (length x depth x width x 0.5233). The location of the dominant fibroid was recorded. Fibroid infarction rate and overall uterine infarction rate were assessed by two observers (AJS, PNML) independently by visual estimation of a decrease in enhancement on MR
images obtained at 3 months follow-up as compared to baseline MR images. Fibroid infarction rates were subsequently classified as 100%, 90-99%, 80-90% and less than 80% (10).

**Embolization procedure**

Bilateral UAE was performed with an unilateral femoral approach. The angiographic endpoint of embolization was a complete occlusion of branches to the perifibroid plexus, leaving the main uterine artery, cervicovaginal branches, and utero-ovarian anastomoses patent (9). During the study period, various brands of microspheres were used with sizes varying of 500-900 µm: Beadblock (Biocompatibles, Farnham, UK), Embospheres (BioSphere Medical, Rockland MA, US) and Embozene (CeloNova BioSciences Newnan, GA, USA). All 712 patients treated with UAE in our hospital received 2 grams of cefazoline intravenously prior to embolization as a general infection prevention. At discharge, patients were advised not to use tampons and to refrain from swimming, taking a bath and sexual intercourse for 6 weeks.

|                     | baseline n=20 | 3 months after UAE n=19* | after mean 20.5 months n=19* |
|---------------------|--------------|--------------------------|-----------------------------|
| symptom severity    | 56           | 23                       | 12                          |
| concern             | 49           | 83                       | 94                          |
| activities          | 59           | 85                       | 96                          |
| energy and mood     | 62           | 82                       | 95                          |
| control             | 63           | 83                       | 97                          |
| sexual activity     | 58           | 82                       | 95                          |
| self-conscious      | 63           | 85                       | 93                          |
| **TOTAL**           | **39**       | **71**                   | **85**                      |

**Table.** UFS-QOL score of 20 women.

* one woman underwent hysterectomy 6 weeks after UAE
**UFS-QOL questionnaire**
Patients were requested to fill out the Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QOL questionnaire) (11) at baseline and 3 months after embolization. In addition, in January 2009 all 20 women filled out a third UFS-QOL questionnaire and a questionnaire with emphasis on complications of the embolization according to the classification by Goodwin et al. (12).

**Data analysis**
Complications were calculated as a percentage with 95% confidence interval (CI) with statistical software (MedCalc statistical software, Mariakerke, Belgium). Mean volume reduction as a percentage of initial volume of the dominant fibroid and uterus was assessed.

**Results**

*Fibroid and uterus volume reduction and infarction rate*
In the 18 patients treated for fibroids the dominant fibroid was located intramural in 17 and submucosal in one. The volume before UAE was 185 cm$^3$ (median 125, range 8-587 cm$^3$) and at 3 months this was 129 cm$^3$ (median 74, range 3-309 cm$^3$). Mean volume reduction of the dominant fibroid thus was 56 cm$^3$ or 30% of the initial mean fibroid volume.

Mean uterus volume before UAE was 386 cm$^3$ (median 343, range 72-902 cm$^3$) and at 3 months this was 289 cm$^3$ (median 188, range 55-858 cm$^3$). Mean volume reduction of the uterus was 97 cm$^3$ or 25% of the initial mean volume.
Mean infarction rate for the dominant fibroid was 97% (median100, range 90-100%) and mean overall uterine infarction rate was 98% (median 100, range 90-100%).

*UFS-QOLs and additional questionnaire*
The third UFS-QOL and the additional questionnaire about adverse events were returned at a mean follow-up interval of 20.5 months (median 16, range 3-65 months) after UAE. The results of the UFS-QOL’s at 3 points in time are displayed in the Table. Improvement occurred in all subscales.
No adverse reactions occurred during hospital stay and none of the 20 patients treated with UAE developed an infectious complication during the 20.5 months follow-up period (0%, 95% confidence interval 0-14%).

One patient underwent a hysterectomy 6 weeks after UAE because of persistent pain without clinical signs of infection. MR imaging showed extensive ischemia of the uterine stroma. Pathological examination confirmed the uterine ischemia without inflammation. Three patients experienced minor adverse events without the need for medical attention: unspecified intermittent pain was reported by 2 patients and the one patient with the submucosal fibroid (diameter 3.7 cm before UAE) had a spontaneous fibroid expulsion without complications.

Discussion

An IUD is the world's most widely used method of reversible birth control, estimated to be used by 160 million women. In large follow-up studies of women with an IUD inserted, the risk of pelvic inflammatory disease attributable to the IUD is very low (less than 1 in 1,300), even in populations with a high prevalence of sexually transmitted infections (13-15). In women with uterine fibroids that become infarcted after UAE, the combination with the presence of a foreign body in the uterine cavity might predispose to infection. This general fear for the combined risks of fibroid infarction and the presence of an IUD is reason for many physicians to remove the IUD before UAE. Conversely, the risk of pelvic inflammatory disease after UAE in the presence of an IUD has never been evaluated; other major studies did not address this topic specifically. Removal of the IUD before UAE has several drawbacks: the timing for replacement of the IUD is not clear and in the meantime other contraceptives have to be used.

In some women with menstrual bleeding disorders (such as from uterine fibroids) a progestagen-releasing IUD is inserted not only for contraception, but also to diminish menstrual bleeding (16). In these cases the removal of the IUD may aggravate menstrual bleeding. In light of these drawbacks of IUD removal and the unknown risks of pelvic inflammatory disease in our practice we have not routinely removed an IUD before UAE and have performed UAE in 20 women with an IUD in situ. In these 20
women, UAE was clinically effective and no IUD related infectious complications occurred at a mean follow-up of over 20 months. It is of note that the protocol of UAE in all women in our series (with or without an IUD in situ) included single dose antibiotics before UAE in combination with life-style guidelines at discharge to prevent infectious complications. The clinical results of UAE in the 20 patients with an IUD in situ in this study are comparable to long-term results of UAE in patients without an IUD in situ treated in our institution (17).

The confidence interval is wide in our limited patient group. Therefore, no definite conclusions can be drawn. However, the results indicate that the risk of pelvic inflammatory disease as a consequence of the IUD in such patients might be limited and might outweigh the disadvantages of removal of the IUD prior to UAE. More studies are needed to confirm these preliminary findings. With more reported cases, clustering the results in a meta-analysis will more precisely indicate the risk with a narrower confidence interval.

In summary, in this limited group of women with symptomatic fibroids treated with UAE and an IUD in situ, no infectious complications occurred. The risk of adverse events related to the removal of an IUD prior to UAE (i.e. pregnancy or aggravation of menstrual bleeding) should be balanced against the probably small risk of pelvic inflammatory disease associated with the presence of an IUD.
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UTERINE ARTERY EMBOLIZATION
IN PATIENTS WITH A
LARGE FIBROID BURDEN:
LONG-TERM CLINICAL AND
MR FOLLOW-UP
Abstract

Purpose
Uterine artery embolization (UAE) in patients with a large fibroid burden is controversial. Anecdotal reports describe serious complications and limited clinical results. We report the long-term clinical and MR results in a large series of women with a dominant fibroid of over 10 cm and/or an uterine volume of over 700 cc.

Methods
Seventy-one consecutive patients (mean age 42.5, median 40, range 25-52 years) with a large fibroid burden were treated by UAE between August 2000 and April 2005. Volume reduction and infarction rate of dominant fibroid and uterus was assessed by comparing baseline and latest follow-up MRI. Patients were clinically followed at various time intervals after UAE with standardized questionnaires.

Results
There were no serious complications of UAE. During a mean follow-up of 48 months (median 59, range 6-106 months) 10 of 71 patients (14%) had a hysterectomy. Mean volume reduction of the fibroid and uterus was 44 and 43%. Mean infarction rate of the fibroid and overall fibroid infarction rate was 86 and 87%. In the vast majority of patients there was a substantial improvement of symptoms. Clinical results were similar in patients with a dominant fibroid over 10 cm and in patients with large uterine volumes by diffuse fibroid disease.

Conclusion
Our results indicate that the risk of serious complications after UAE in patients with a large fibroid burden is not increased. Moreover, clinical long-term results are as good as in other patients that are treated with UAE. Therefore, a large fibroid burden should not be considered a contra-indication for UAE.
Introduction

Uterine artery embolization (UAE) is an accepted alternative to surgery in the management of symptomatic patients with uterine fibroids (1-7). However, the role of UAE in symptomatic women with a large fibroid burden is subject to debate. In several small studies, response to UAE was judged insufficient in patients with a large fibroid over 8 cm with a higher rate of need for additional therapy after UAE (8,9). In addition, there is general unspecified fear of an excessive effect after embolization in these patients due to rapid ischemia and necrosis. This fear is based on several early case reports describing rare but serious complications shortly after UAE for large fibroids such as unbearable pain, infection, septic uterine necrosis and lethal sepsis (10-12). On the other hand, some studies suggest that results of UAE in patients with a large fibroid burden are as good as in other patients with symptomatic fibroids with comparable low rates of serious complications (13-15). However, long-term follow-up studies in this special subset of patients have not been performed to date. In this study we retrospectively evaluated the long-term results of UAE in symptomatic women with large fibroid burden.

Material and methods

Patients

This retrospective study was approved by the Institutional Review Board with a waiver for informed consent. From an institutional database with prospectively collected data of 431 women with symptomatic uterine fibroids treated with UAE between August 2000 and April 2005, 71 consecutive women were selected with a large fibroid burden defined as a dominant fibroid with a longest axis larger than 10 cm and/or a uterine volume of more than 700 cc. Diagnosis of uterine fibroid disease was established by history, clinical gynecological examination and MR imaging. All women had previous medical therapies for their complaints without sufficient clinical results. Exclusion criteria for UAE were pregnancy, pelvic inflammatory disease, gynecological malignancy, pure adenomyosis and thin-stemmed pedunculated fibroids. All 71 women were premenopausal with a mean age of 42.5 years (median 40, range 25-52 years). Presenting symptoms of 71 women were bleeding in 60 (85%), pain in 41
(58%) and bulk-related symptoms in 64 (90%). Of 71 women, 42 (59%) had a fibroid larger than 10 cm and 30 of these 42 women had an overall uterus volume of more than 700 cc. The remaining 29 women (41%) had an uterus volume of more than 700 cc but no fibroid larger than 10 cm.

Patients are categorized in 3 subgroups. Group A: patients with a dominant fibroid diameter of over 10 cm and a uterine volume less than 700 cc (A: > 10 cm, < 700 cc). Group B: patients with a dominant fibroid of over 10 cm and an uterine volume of over 700 cc (B: > 10 cm, > 700 cc). Group C: patients with an uterine volume of over 700 cc and with fibroids smaller than 10 cm (C: < 10 cm, > 700 cc). Presenting symptoms of the subgroups of patients are displayed in Table 1.

|        | Bleeding | Pain | Bulk-related symptoms |
|--------|----------|------|-----------------------|
| **A**  | >10cm 700cc | N= 12 |                       |
|        | 9        | 6    | 11                    |
| **B**  | >10cm >700cc | N= 30 |                       |
|        | 25       | 16   | 26                    |
| **C**  | <10cm >700cc | N= 29 |                       |
|        | 26       | 19   | 27                    |
| **All** |          |      |                       |
|        | **60**   | **41** | **64**               |

**Table 1.** Presenting symptoms of 71 patients with a large fibroid burden in 3 subgroups.
**MR imaging at baseline and follow-up**

All patients had native and contrast enhanced MRI prior to embolization and at various intervals post embolization. From baseline MRI, the dimensions and volumes of the fibroids and uterus were assessed. Volume calculation was done by using the formula of a prolate ellipse \((\text{length} \times \text{depth} \times \text{width} \times 0.5233)\). Dominant fibroid infarction rate and overall fibroid infarction rate after UAE were assessed by two observers in consensus on latest MRI by visual estimation of decrease in enhancement as compared to baseline MRI as described by Siskin (16). Infarction of less than 80% was considered insufficient.

**Embolization procedure**

UAE was performed after selective catheterization of both uterine arteries via a unilateral approach. The use of a microcatheter was left to the discretion of the physician. In women who desired future pregnancy, embolization was performed simultaneously on both sides to limit radiation exposure. Various embolic agents (Contour SE, EmboGold, Bead Block and Embosphere Microspheres) ranging in size of 500–900 microns were used. The endpoint was a complete occlusion of arteries to the peri-fibroid plexus, with sluggish flow in the ascending segment of the uterine artery, and leaving the main uterine artery, cervico-vaginal branches, and utero-ovarian anastomoses patent (17). Complications were recorded.

**Clinical follow-up**

Baseline clinical status was assessed by an interview using a standardized questionnaire on patient’s symptoms of bleeding, pain and bulk. At various time intervals after UAE patients returned for a follow-up MRI and an interview by a nurse practitioner to assess the evolution of symptoms using the same questionnaire. For the purpose of this study, in July 2009 all women were requested to fill out the validated Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QOL) (18). In addition, women were asked to fill out the standardized questionnaire aiming at the long-term evolution of their baseline symptoms, additional therapy and adverse events such as vaginal dryness and discharge, menopausal complaints or fibroid expulsion. In women who did not return the questionnaire of July 2009, data of the latest previously available follow-up interval were considered final result.
Data analysis
Complications were expressed as a proportion. The fibroid diameter change during follow-up and the rate of uterine volume reduction were assessed for all patients and the 3 subgroups by comparison of the latest MRI with baseline. Volume reduction of large fibroid and uterus was calculated as a proportion of initial volume. Differences in volume reduction of dominant fibroid and uterus and differences in infarction rates were evaluated between the 3 subgroups. Chi-square test or Fisher’s exact test was used for comparison of proportions and t-test for comparison of means. P-values < 0.05 were considered significant. Statistical analysis was done with MedCalc statistical software (MedCalc, Mariakerke, Belgium).

Results

Imaging results
Mean MR imaging follow-up was 13.8 months (median 12, range 4-47 months). The dominant fibroid diameter and volume reduction, uterine volume reduction and infarction rates of the dominant fibroid and overall fibroid infarction rate for all patients and the 3 subgroups are displayed in Table 2 and a representative image in Figure 1. After UAE, mean infarction rates of both the dominant fibroid and the overall fibroid infarction rate were high (85-90%) in all 3 subgroups. On individual base, in 20 of 71 patients (28%) the infarction rate was considered insufficient with less than 80%. One patient had recurrent symptoms without additional therapy, and 8 patients had good clinical results despite the insufficient infarction rate. The remaining 11 patients had additional therapy during follow-up.

Adverse events
Adverse events were reported by 21 patients (29.5%). Transient amenorrhea occurred in 5 women and permanent amenorrhea in another 5 (one 43 year old woman and 4 women older than 47 years). One woman reported a fibroid expulsion 2 months after UAE, 3 reported fibroid sloughing and 2 had vaginal discharge. Three women needed additional pain medication. Three women developed an unspecified urogenital infection successfully treated with antibiotics. None of the patients developed a severe post embolic syndrome. There was no emergency surgery after UAE.
Table 2. Baseline of 71 patients and follow-up MR findings of 70 patients with large fibroid burden treated with UAE, including results per subgroup.

| Dominant fibroid diameter Baseline (mean and range) | Dominant fibroid diameter follow-up (mean and range) | Dominant fibroid diameter reduction | Dominant fibroid volume Baseline (mean and range) | Dominant fibroid volume follow-up (mean and range) | Dominant fibroid volume reduction | Uterine volume Baseline (mean and range) | Uterine volume follow-up (mean and range) | Uterine volume reduction | Dominant fibroid infarction rate (mean and range) | Overall fibroid infarction rate (mean and range) |
|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------|-----------------------------------------------|-------------------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------------------|---------------------------------|------------------------------------------|------------------------------------------|
| A >10cm, <700cc N=12                                |                                                      |                                   |                                               |                                                 |                                   |                                   |                                               |                                 |                                         |                                         |
| 10.6 cm 10-13 cm                                   | 7.7 cm 6.4-9.5 cm                                   | 27%                               | 379 cm³ 297-547 cm³                           | 177 cm³ 68-254 cm³                              | 53%                               | 591 cm³ 471-691 cm³                  | 385 cm³ 225-621 cm³                  | 35%                             | 90% 40-100%                             | 80% 50-100%                             |
| B >10cm, >700cc N=30                               |                                                      |                                   |                                               |                                                 |                                   |                                   |                                               |                                 |                                         |                                         |
| 12.6 cm 10-16 cm                                   | 9.4 cm 6.0-13.4 cm                                  | 25%                               | 723 cm³ 417-1265 cm³                          | 353 cm³ 79-1127 cm³                            | 51%                               | 1358 cm³ 788-3037 cm³               | 760 cm³ 134-1796 cm³               | 44%                             | 85% 20-100%                             | 85% 20-100%                             |
| C <10cm, >700cc N=29                               |                                                      |                                   |                                               |                                                 |                                   |                                   |                                               |                                 |                                         |                                         |
| 7.9 cm 4.3-9.6 cm                                  | 6.5 cm 3.4-9.6 cm                                   | 18%                               | 199 cm³ 42-424 cm³                            | 131 cm³ 18-343 cm³                             | 34%                               | 1105 cm³ 653-1855 cm³              | 620 cm³ 58-1526 cm³               | 45%                             | 90% 40-100%                             | 90% 50-100%                             |
| All N=71                                            |                                                      |                                   |                                               |                                                 |                                   |                                   |                                               |                                 |                                         |                                         |
| 10.3 cm 4.3-16 cm                                  | 8 cm 3.4-13.4 cm                                   | 22%                               | 450 cm³ 42-1265 cm³                           | 233 cm³ 18-1127 cm³                            | 44%                               | 1125 cm³ 471-3037 cm³              | 639 cm³ 58-1796 cm³               | 43%                             | 86% 20-100%                             | 87% 20-100%                             |
Figure 1. Sagittal contrast enhanced MRI in a 31 year old woman before (A) and 13 months after (B) uterine artery embolization for a solitary 12 cm fibroid. After embolization, the fibroid is completely infarcted with a volume reduction of 60%.

Table 3. Additional therapy after UAE during mean follow-up of 48 months in 71 patients with large fibroid burden and in the 3 subgroups.
**Additional therapy during the follow-up**

During a follow-up of mean 48 months (median 59, range 6-106 months), 18 of 71 patients (25%) underwent additional therapy. The distribution of patients with additional therapy in the 3 subgroups is displayed in Table 3. Eight women had a second embolization. In 6 of 8 women fibroids were initially completely devascularized but showed revascularization on later MRI. In the other 2 women the fibroids were initially not completely devascularized due to additional vascular supply from the ovarian artery and the inferior mesenteric artery (Fig. 2); this could be corrected in the repeat embolization. After repeat UAE all fibroids remained devascularized on subsequent MRI.

Ten women had a hysterectomy due to insufficient relief of clinical symptoms. In one patient, with fever and vaginal discharge, a hysterectomy was performed early at 7 weeks after UAE. Pathological examination showed normal uterine stroma without signs of necrosis. In one patient hysterectomy was performed after recurrence of symptoms 4 years after UAE.

*Figure 2.* Angiogram 14 months after insufficient result of first embolization in a 44 year old woman with large fibroid burden demonstrates substantial additional vascular supply to the uterus from the inferior mesenteric artery, not appreciated on first embolization.
Evolution of presenting symptoms

The late follow-up questionnaire in July 2009 was returned by 44 of 71 patients (62%) and these patients had a mean follow-up duration of 68 months (median 73, range 48-106 months). Of these 44 patients, 13 had additional therapies and were censored from final follow-up. The long-term evolution of symptoms in the remaining 31 patients is given in Table 4. The second part of the questionnaire, the UFS-QOL was filled out by 35 of the 44 patients: 7 patients had a hysterectomy, 1 a second embolization and one patient was menopausal at the age of 54, 6 years after UAE. Results are presented in Table 5. After UAE the symptom severity score and the health-related quality-of-life (HRQL) total score of our patient group is within range of normal women; scores for the other subscales are in the range of mildly symptomatic patients. Of the 71 patients, 27 patients did not return the long-term questionnaire and had a shorter mean follow-up of 14 months (median 12, range 6-40 months). In 5 of 27 patients additional therapies were performed. Evolution of symptoms of the remaining 22 women is given in Table 6.

Data analysis

Statistical evaluation of the differences in dominant fibroid volume reduction, uterine volume reduction and infarction rates between the 3 subgroups did not show significant results.

|        | Bleeding | Pain | Bulk-related symptoms |
|--------|----------|------|-----------------------|
| A >10cm, <700cc N=6 | 4 of 4 improved | 3 of 3 improved | 6 of 6 improved |
| B >10cm, >700cc N=13 | 11 of 11 improved | 6 of 6 improved | 13 of 13 improved |
| C <10cm, >700cc N=12 | 4 of 4 improved | 3 of 3 improved | 6 of 6 improved |
| All N=31 | 19 of 19 improved | 12 of 12 improved | 25 of 25 improved |

Table 4. Long-term clinical follow-up results after mean 68 months in 31 patients treated with UAE for large fibroid burden who returned the late questionnaire and had no additional therapy.
| Symptom severity | Concern | Activities | Energy Mood | Control | Self conscious | Sexual function | HRQL total |
|------------------|---------|------------|-------------|---------|----------------|-----------------|------------|
| A >10cm,<700cc N=7 | 17.4 | 78.6 | 75 | 69.9 | 72.9 | 78.6 | 58.9 | 86.6 |
| B >10cm, >700cc N=16 | 12.1 | 62.6 | 66.9 | 84.8 | 66.3 | 59.5 | 65 | 84.6 |
| C <10cm, >700cc N=12 | 22.5 | 87.3 | 94.2 | 95.8 | 94.1 | 91.7 | 81.8 | 92.5 |
| All N=35 | 16.6 | 72.1 | 75.4 | 82.8 | 74.7 | 72.1 | 67.3 | 87.7 |

Table 5. UFS-QOL after mean 68 months in 35 patients treated with UAE for large fibroid burden who returned the late questionnaire and had no additional therapy.

| Bleeding | Pain | Bulk-related symptoms |
|----------|------|-----------------------|
| A >10cm, <700cc N=3 | 3 of 3 improved | 1 of 1 improved | 2 of 2 improved |
| B >10cm, >700cc N=8 | 5 of 6 improved | 1 of 3 improved | 5 of 6 improved |
| C <10cm, >700cc N=11 | 7 of 8 improved | 9 of 10 improved | 8 of 10 improved |

Table 6. Clinical follow-up after mean 14 months in 22 patients treated with UAE for large fibroid burden who did not return the late questionnaire and had no additional therapy.
Discussion

Uterine artery embolization is at the present time gaining acceptance as an alternative to hysterectomy or myomectomy in symptomatic women with uterine fibroids. Many women appreciate the results that can be obtained with UAE: improvement or elimination of symptoms and reduction of uterine size while retaining the uterus and preservation of fertility. In many studies the good long-term results and low complication rates of this treatment are reported (5-7). Despite these overall satisfying results, in the subgroup of patients with a large fibroid burden a higher rate of serious ischemic, necrotic and infectious complications is ascribed based on several anecdotal reports (9-11).

Our results show that a large fibroid burden does not decrease the efficacy of UAE and there is no higher complication rate. Our results in patients with a large fibroid burden are comparable and in the same range as in large studies reporting on results of UAE in unselected patients (6,7). In the vast majority of our patients there is a significant volume reduction of the fibroids in combination with good clinical results.

The rate of adverse events after UAE in patients with a large fibroid burden was very low and emergent surgery was never necessary. These results are valid for patients with a very large dominant fibroid, as well as for patients with a large uterine volume from many smaller fibroids or the combination. During long-term follow-up, the frequency of additional embolization and hysterectomy in our selected patients was in the same range as in previous studies on unselected patients (6). Our findings suggest that in women with a large fibroid burden, who are reluctant to hysterectomy, UAE is a valuable alternative with a high rate of success in preserving the uterus.

Our study has several limitations. Long-term clinical follow-up was not available in all patients. The UFS-QOL was only assessed at long-term follow-up and not at baseline. However, a strong point of our study was the follow-up duration of over 5 years in the majority of patients and the complete clinical follow-up in terms of additional treatments. Our study is the first study on UAE in patients with a large fibroid burden in a large patient group and with long-term follow-up. Several studies on limited patient groups and shorter follow-up have reported similar good results as ours (13,14).
Some authors consider a large fibroid burden a risk factor for serious complications such as infections and ischemic uterine injury requiring emergent hysterectomy and it is advocated that UAE should not be performed for multiple fibroids larger than 10 cm in diameter or a large uterine volume. However, the presumption to refrain from UAE in these patients is based on a few early case reports describing serious complications (9,11). Katsumori was the first to report on results of UAE in 47 patients with large fibroids as part of a cohort of 152 patients with a mean follow-up of 17 months (19). The conclusion of this study was that there was no increased risk to patients undergoing UAE for fibroids on the basis of size. Later, these good results were confirmed in a smaller study with a limited follow-up of 12 months (13).

In conclusion, our results confirm previous reports that the risk of serious complications after UAE in patients with large fibroids is not increased. Moreover, clinical long-term results are as good as in other patients with symptomatic fibroids treated with UAE. Therefore, a large fibroid burden should not be considered a contra-indication for UAE.
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GENERAL DISCUSSION
AND SUMMARY
General discussion

In 1995 Ravina was the first to describe the effect of uterine artery embolization (UAE). In the years that followed numerous observational clinical studies on the technique and clinical results of embolization have been published. In these studies UAE was effective in substantially reducing the fibroid size (on average by 50–60%) as well as reducing bleeding and other fibroid-related symptoms both on short and long-term follow-up. In 2005 and 2007 two unmasked randomized controlled trials (EMMY and REST) comparing UAE and hysterectomy were published that confirmed that UAE was effective and thus hysterectomy could be avoided in the vast majority of patients. The favorable results of UAE in these randomized trials resulted in rapid widespread acceptance of UAE as an alternative for hysterectomy.

Technique of uterine artery embolization

The technique of UAE is in constant evaluation. Our results indicate that complete occlusion of the uterine arteries with the inherent risk of reflux of embolic material in vessels causing ischemic damage to normal structures is not necessary. An embolization technique limited to the arteries supplying the perifibroid plexus provides comparable complete infarction rate of the fibroids with a lower risk of complications. Also the clinical results of the limited embolization technique in terms of reduction of bleeding, bulk and pain are comparable to studies that used the conventional technique. Our results also indicated that the use of calibrated gelatine microspheres for UAE is effective and safe. Microcatheter blockage did never occur with this new embolic agent. Clinical and imaging results were comparable to studies in which other agents were used.

Results on follow-up

Our results of follow-up of patients with fibroids treated with UAE demonstrate that the good short-term results of UAE are maintained on the longer term, up to 7 years after embolization. During follow-up, about a quarter of women need additional treatment in the form of additional embolization or hysterectomy due to insufficient symptom relief. Predictors of failure on the long-term were a lack of improvement in bleeding or pain at
one year after UAE and the percent reduction in dominant tumor volume. The vast majority of women undergoing UAE is satisfied with the treatment result, also on the long-term.

**Contra-indications for uterine artery embolization**

Since the introduction of UAE, several clinical and anatomical factors have been considered a contra-indication: pedunculated fibroids, a large fibroid burden and the presence of an IUD. However, this presumption was based on general fear, isolated case reports and the opinion of several experts without systematic validation. In this thesis it is demonstrated that UAE can be performed safely in patients with pedunculated fibroids, in patients with a large fibroid burden and in patients with an IUD in situ. In these patient groups, there were no complications that could have been attributed to these factors and clinical results were similar as in other patients. Therefore, pedunculated fibroids, a large fibroid burden and the presence of an IUD should not be considered risk factors for additional complications.

**Future perspectives**

In the near future, wider implementation of UAE is necessary. UAE should be offered to all patients suitable for this technique. This can be primarily achieved through training and certification. In addition, the results of current research should be transformed in national and international guidelines for treatment of women with symptomatic fibroids. An important clinical issue, that is not yet elucidated, is the preservation of fertility after UAE in comparison to myomectomy. This subject should be addressed in a new randomized trial.
Summary

In Chapter 1 a general introduction is provided.

In Chapter 2 the technique of UAE is described. Since the introduction of UAE the applied embolization technique underwent several refinements. First complete blockage of both uterine arteries was the goal to obtain complete fibroid devascularization. Later more sophisticated targeted embolization of the fibroid itself with preservation of cervical branches, vaginal branches and ovarian anastomoses has gained more widespread acceptance. In addition, calibrated microspheres gradually replaced polyvinyl alcohol particles as embolic agents. In this chapter, an updated overview on modern uterine fibroid targeted embolization techniques is given, including an outline on catheterization related problems, flaws and tricks.

In Chapter 3 the efficacy and safety of precisely calibrated microspheres used for UAE in women with symptomatic uterine fibroids is evaluated. Between August 2006 and August 2008, 86 consecutive premenopausal women were treated with UAE. Embolization was performed via a bilateral femoral approach using two microcatheters. Calibrated microspheres of 500, 700 and 900 µm alone or in combination were used as embolic agent. MRI was used to assess the change in uterine and dominant fibroid volume as well as dominant fibroid and overall infarction rate. Clinical follow-up was evaluated by the Uterine Fibroids Severity and Quality of Life questionnaire (UFS-QOL) at baseline, at 3 months and in November 2008 after a mean follow-up of 12.8 months. The UFS-QOL showed significant improvement in both symptom severity and quality of life after 3 months and continued to improve at last follow-up of mean 12.8 months. The use of precisely calibrated microspheres for UAE is effective and safe. Microcatheter blockage did not occur. Clinical and imaging results are comparable to studies in which other microspheres are used.

In Chapter 4 we assessed the safety and efficacy of a limited UAE using large calibrated tris-acryl gelatin microspheres (CTGM). Two different embolic agents were used in this study. It was confirmed that a limited UAE using CTGM in symptomatic women has a low risk of procedural complications with good clinical and MR imaging results at follow-up. Relief of clinical symptoms, patient satisfaction, adverse events,
and uterine and fibroid volume reduction were in the same range as those in previous studies that used polyvinyl alcohol particles as embolic agent. Our results were also comparable with those of studies reporting on the use of CTGM with shorter follow-up. The results of this study confirmed the known limitations of UAE in the treatment of symptomatic uterine fibroids: 7.6% of patients needed additional therapy and 7% of patients were unsatisfied with the results.

In Chapter 5 we evaluated the mid-term clinical results and patient satisfaction following UAE in 135 women with symptomatic fibroids treated between August 1998 and December 2002. In January 2003 all patients were asked to fill in a questionnaire aimed at changes in bleeding, pain and bulk-related symptoms. Symptoms after UAE were scored as disappeared, improved, unchanged or worsened. Adverse events and patient satisfaction after UAE were recorded according to accepted methods. The questionnaire was returned by 110 of 135 women (81%) at a median time interval of 14 months following UAE. In 10 women additional embolization or hysterectomy had been performed. Of the 110 responders, 86 (78%) were satisfied with the result of UAE. We concluded that UAE in women with symptomatic uterine fibroids leads to substantial improvement of symptoms. Patient satisfaction is good in the vast majority after a median follow-up period of 14 months.

In Chapter 6 the long-term outcomes after UAE and factors associated with treatment failure in 100 women with symptomatic uterine leiomyomas were evaluated. Clinical outcome data (changes in symptoms, menstrual status, and the need for subsequent therapies) and satisfaction data were collected. Treatment failure was defined by the need for subsequent surgery (hysterectomy or myomectomy), the need for a second embolization, or a lack of symptom improvement at the patient’s final follow-up interval. Possible predictors of treatment failure were age, clinical baseline symptoms (bleeding, pain, and bulk), and imaging results (proportion volume reduction of the dominant tumor). Follow-up was available in 93 women (median follow-up 54 months; range 45–87 y). Continued symptom relief was observed in 72% of patients (n=67). Among the 26 women with treatment failure (28%), 11 (42%) underwent hysterectomy, 4 (15%) myomectomy, and 8 (31%) repeat embolization. Three (12%) reported no improvement. In women without any additional surgery (n=70), heavy menstrual
bleeding, pain, and bulk-related symptoms improved in 97%, 93%, and 92%. Ninety percent of all women (n= 93) were satisfied or very satisfied at final follow-up. Predictors of failure on the long-term were a lack of improvement in bleeding or pain at one year after UAE and the percent reduction in dominant tumor volume. We concluded that UAE in women with symptomatic fibroids leads to long-term symptom improvement.

In Chapter 7 we retrospectively assessed the complications and outcomes of UAE in 29 women with 31 pedunculated fibroids in a large single center patient cohort. MRI prior to embolization and at 3 months was used to calculate stalk diameter change and volume reduction of both pedunculated fibroid and uterus. Complications were recorded and long-term clinical follow-up (mean 33 months) was assessed by a questionnaire. Mean uterine and pedunculated fibroid volume reduction was 37% and 33%. Mean stalk diameter reduction was 0.3 cm or 13% from initial mean diameter. Stalk enhancement was not affected by UAE. Mean pedunculated fibroid infarction and mean overall infarction rate were for observer 1; 87% and 92% and for observer 2; 88% and 92% with good inter-observer variability. All women returned the questionnaire and no early or late complications of UAE were reported. In this small series of pedunculated subserosal fibroids treated with UAE, no complications occurred. Our findings suggest that treatment of pedunculated fibroids with UAE may be safe and effective.

In Chapter 8 we retrospectively evaluated the occurrence of infectious complications following embolization in 20 women with symptomatic uterine fibroids and an intrauterine device (IUD) in situ. At baseline and 3 months after UAE, MR imaging was performed and the UFS-QOL was filled out. In January 2009 (mean follow-up 20.5 months) all patients responded to a third UFS-QOL questionnaire and an additional questionnaire with emphasis on adverse events and infectious complications. One patient underwent a hysterectomy 6 weeks after UAE because of persistent pain. Three patients experienced minor adverse events without the need for medical attention. In none of the patients infections developed. UFS-QOL scores improved from 39 at baseline to 85 at last follow-up. We concluded that the presence of an IUD might not be considered a contra-indication for UAE.
In Chapter 9 we report the long-term clinical and MR results in 71 women with a dominant fibroid of over 10 cm and/or an uterine volume of over 700 cc treated with UAE between August 2000 and April 2005. Volume reduction and infarction rate of dominant fibroid and uterus was assessed by comparing baseline and latest follow-up MRI. Patients were clinically followed at various time intervals after UAE with standardized questionnaires. There were no serious complications of UAE. During a mean follow-up of 48 months, 10 of 71 patients (14%) had a hysterectomy. Mean volume reduction of the fibroid and uterus was 44 and 43%. Mean infarction rate of the fibroid and overall fibroid infarction rate was 86 and 87%. In the vast majority of patients there was a substantial improvement of symptoms. Clinical results were similar in patients with a dominant fibroid over 10 cm and in patients with large uterine volumes by diffuse fibroid disease. Our results indicated that the risk of serious complications after UAE in patients with a large fibroid burden is not increased. Moreover, clinical long-term results are as good as in other patients that are treated with UAE. Therefore, a large fibroid burden should not be considered a contra-indication for UAE.
ALGEMENE DISCUSSIE EN SAMENVATTING

DANKWOORD

CURRICULUM VITAE
Algemene discussie

In 1995 was Ravina de eerste die de resultaten van Uterus Embolisatie (UE) bij vrouwen met symptomatische vleesbomen heeft beschreven. In de daarop volgende jaren zijn talrijke wetenschappelijke artikelen verschenen over de techniek en de klinische resultaten van UE. UE bleek effectief te zijn in het verkleinen van de vleesbomen (gemiddeld met 50-60%) en het reduceren bloedverlies en andere klinische symptomen zowel op korte als lange termijn.

In 2005 en 2007 zijn 2 gecontroleerde studies (EMMY en REST) gepubliceerd die UE vergeleken met operatieve baarmoederverwijdering; hierin werd aangetoond dat UE effectief en veilig was en dus kan baarmoederverwijdering worden vermeden in de meeste patiënten. De gunstige resultaten van UE in deze studies resulteerden in een brede acceptatie van UE als alternatief voor baarmoederverwijdering.

Techniek van uterus embolisatie

De techniek van UE wordt voortdurend verfijnd en bijgesteld. Onze resultaten tonen dat complete afsluiting van de arteria uterina met het bijbehorende risico op reflux van embolisatie materiaal in vaten naar normale structuren met kans op ischemische schade niet nodig is. Volstaan kan worden met het afsluiten van de vaten naar de vleesbomen zelf. Deze gelimiteerde embolisatie techniek leidt eveneens tot complete infarcering van de vleesbomen, met een veel kleiner risico op bijkomende ischemische schade. De klinische resultaten zoals verminderen van bloedingen, bulk symptomen en pijn zijn vergelijkbaar met die van de conventionele techniek. Onze resultaten geven eveneens aan dat het gebruik van gekalibreerde gelatine microsferen voor UE effectief en veilig is. De microkatheter raakte met dit materiaal nooit verstopt.

Resultaten van vervolg onderzoek

Onze bevindingen bij langer klinisch vervolg onderzoek bij vrouwen met symptomatische vleesbomen die behandeld zijn met UE tonen dat de goede resultaten op de korte termijn goed standhouden op de lange termijn, tot 7 jaar na UE. Na UE is in ongeveer een kwart van de behandelde vrouwen het klinisch resultaat onvoldoende waardoor een aanvullende embolisatie of operatieve baarmoederverwijdering
noodzakelijk is. Voorspellende factoren voor onvoldoende resultaat op de lange termijn zijn een uitblijven van verbetering na 1 jaar en een beperkte afname van het volume van de vleesboom na UE. Van alle vrouwen behandeld met UE is heeft driekwart de baarmoeder kunnen behouden en is tevreden met het resultaat op de langere termijn.

Contra-indicaties voor uterus embolisatie

Vanaf de introductie in de klinische praktijk van UE voor symptomatische vleesbomen werden verschillende klinische en anatomische factoren beschouwd als een contra-indicatie voor deze behandeling: gesteelde vleesbomen, een grote vleesboom last en de aanwezigheid van een spiraaltje in de baarmoeder. Deze contra-indicaties waren gebaseerd op algemene angst, geïsoleerde gevallenbeschrijvingen en op de mening van verschillende experts, niet op gedegen klinisch onderzoek. Ons onderzoek bij zulke patiënten laat zien dat UE in deze patiëntengroep veilig en effectief is. In onze handen waren er geen extra complicaties die zouden kunnen worden toegeschreven aan de eerder genoemde factoren. Dus, gesteelde fibromen, een grote vleesboom last en de aanwezigheid van een spiraaltje vormen geen contra-indicatie voor UE.

Toekomst perspectief

In de nabije toekomst is een bredere invoering van UE in meer ziekenhuizen noodzakelijk om alle vrouwen met symptomatische vleesbomen die hiervoor in aanmerking komen te kunnen behandelen. Dit kan worden bereikt door training en certificering. Tevens moeten de klinische wetenschappelijke resultaten worden aangewend voor het opstellen van behandelings richtlijnen voor vrouwen met symptomatische vleesbomen. Een belangrijk klinisch vraagstuk dat nog niet is opgehelderd betreft het behoud van fertiliteit na UE in vergelijking met myomectomy. Dit vraagstuk zou het onderwerp moeten worden van een nieuwe gerandomiseerde studie.
Samenvatting

In hoofdstuk 1 wordt een algemene inleiding gegeven.

In hoofdstuk 2 wordt de techniek van uterus embolisatie (UE) besproken. Sinds de introductie van UE is de toegepaste techniek steeds verder verbeterd. In de beginjaren was een complete afsluiting van beide ateriae uterina het doel om gehele devascularisatie van de vleesboom te verkrijgen. Later werd meer en meer een verfijnde techniek toegepast met een doelgerichte embolisatie van de vleesboom zelf waarbij de arteriën naar de baarmoederhals, de vagina en anastomosen naar de eierstokken gespaard blijven. In dit hoofdstuk wordt een update gegeven van de moderne embolisatie techniek met een samenvatting van katheterisatie problemen en praktische tips.

In hoofdstuk 3 wordt de doelmatigheid en veiligheid van UE, met gebruik van homogeen gekalibreerde gelatine microsferen, bij vrouwen met symptomatische vleesbomen geëvalueerd. Van augustus 2006 tot augustus 2008 werden 86 premenopauzale vrouwen met UE behandeld. De embolisatie werd uitgevoerd door punctie van beide liesarteriën en het gebruik van microkatheters. Als embolisatie materiaal werden gekalibreerde microsferen van alleen 500, 700 en 900 µm of een combinatie hiervan gebruikt. De verandering in het volume van de dominante vleesboom en de baarmoeder en de mate van infarcering hiervan werd bepaald aan de hand van MR beelden. Het klinische resultaat werd geëvalueerd met behulp van de Uterine Fibroids Severity and Quality of Life (UFS-QOL) vragenlijst voor UE, 3 maanden erna en in november 2008. De UFS-QOL liet na 3 maanden een significante verbetering zien van zowel de ernst van de symptomen als de kwaliteit van leven. Deze verbetering zette door tot aan het laatste vervolgonderzoek na gemiddeld 12,8 maanden. Het gebruik van homogeen gekalibreerde microsferen voor UE is effectief en veilig. Er was geen blokkade van de microkatheter. De klinische en radiologische resultaten zijn vergelijkbaar met studies waarin andere microsferen werden gebruikt.
In hoofdstuk 4 onderzochten wij de veiligheid en effectiviteit van een tot de vleesbomen zelf gelimiteerde UE met grote gekalibreerde gelatine microsferen. In deze studie werden 2 embolisatie materialen gebruikt. Bevestigd werd dat een gelimiteerde embolisatie met gekalibreerde microsferen bij symptomatische vrouwen een laag complicatierrisico heeft met goede klinische en MR beeldvorming resultaten bij vervolg onderzoek.

Afname van klinische symptomen, patiënttevredenheid, het voorkomen van nadelige effecten en de afname van het volume van baarmoeder en vleesboom waren gelijk aan studies waarin gebruik gemaakt werd van polyvinyl alcohol partikels, het tot dan toe meest gebruikte embolisatie materiaal. Onze resultaten waren vergelijkbaar met studies met een kortere vervolgduur. De resultaten van deze studie lieten ook de tekortkomingen van UE zien: 7.6% van de patiënten had later nog een aanvullende behandeling nodig en 7% van de patiënten was niet tevreden met het klinische resultaat.

In hoofdstuk 5 beoordeelden we de middellange termijn resultaten en klinische tevredenheid na UE bij 135 vrouwen met symptomatische vleesbomen die behandeld waren van augustus 1998 tot augustus 2002. In januari 2003 werden alle patiënten gevraagd een vragenlijst in te vullen, gericht op veranderingen in bloedingspatroon, pijn en symptomen van massa-effect. Het beloop van symptomen na UE werd geregistreerd als verdwenen, verbeterd, ongewijzigd of verslechterd. Nadelige effecten en patiënttevredenheid na UE werden vastgelegd. De vragenlijst werd door 110 van de 135 vrouwen (81%) terug gestuurd na een mediane periode van 14 maanden. Tien vrouwen hadden in de tussentijd een 2e embolisatie of baarmoeederverwijdering ondergaan. Zesentachtig (81%) van de 110 vrouwen waren tevreden met het resultaat van de UE. Wij constateerden dat UE bij vrouwen met symptomatische vleesbomen leidt tot vermindering van klachten en dat de meerderheid van de patiënten tevreden is na 14 maanden.

In hoofdstuk 6 evaluerden we de lange termijn resultaten van UE bij 100 vrouwen met symptomatische vleesbomen en factoren geassocieerd met falen van de behandeling. Klinische behandelings resultaten (zoals verandering van symptomen,
menstruatiestatus, aanvullende behandelingen) en patiënttevredenheid werden geregistreerd. Aanvullende chirurgische behandeling (bijvoorbeeld baarmoederwijdering of verwijdering van een vleesboom), een tweede embolisatie of een gebrek aan klinische verbetering werd gedefinieerd als behandelingsfalen. Mogelijke factoren die behandelingsfalen voorspellen waren de leeftijd van patiënten, klinische uitgangswaarden (bijvoorbeeld bloeding, pijn, massa-effect) en de resultaten van de MR beeldvorming (bijvoorbeeld het percentage volume afname van de dominante vleesboom).

Vervolg onderzoek was beschikbaar bij 93 vrouwen (mediane vervolgduur, 54 maanden; spreiding 45–87 maanden). Afname van symptomen werd vastgesteld bij 72% van de patiënten (n=67). Bij 26 vrouwen (28%) had de behandeling gefaald; bij 11 vrouwen (42%) was de baarmoeder verwijderd, bij 4 vrouwen (15%) was de vleesboom verwijderd en 8 vrouwen (31%) hadden een tweede embolisatie ondergaan. Drie vrouwen (12%) gaven aan geen verbetering te hebben ervaren na UE. Bij vrouwen zonder aanvullende behandeling (n=70) nam het bloedverlies af in 97%, pijn nam af in 93% en het massa-effect verbeterde in 92%. Negentig procent van de vrouwen was tevreden of zeer tevreden bij de laatste controle. Gebrek aan afname van de bloedingen, pijn 1 jaar na UE en het percentage van volume afname van de dominante vleesboom hadden een voorspellende waarde voor behandelingsfalen. We constateerden dat UE bij vrouwen met symptomatische vleesbomen leidt tot een langdurige vermindering van klachten.

In hoofdstuk 7 beoordeelden wij retrospectief de complicaties en resultaten van UE bij 29 behandelde vrouwen met 31 gesteelde vleesbomen. Met behulp van MR voor en 3 maanden na embolisatie werd de verandering van de diameter van de steel van de vleesboom en de volume afname van zowel de gesteelde vleesboom als de baarmoeder berekend. De complicaties werden vastgelegd en het lange termijn klinische resultaat (na gemiddeld 33 maanden) werd beoordeeld aan de hand van een vragenlijst.

De gemiddelde afname van het volume van de baarmoeder en van de gesteelde vleesboom was 37% en 33%. De gemiddelde afname van de steel was 0.3 cm of 13% van de uitgangsdiameter van de steel. De aankleuring van de steel bleef na UE intact. De gemiddelde infarcering van de gesteelde vleesboom en de algemene baarmoeder
infarcering waren voor beoordelaar 1 87% en 92% en voor beoordelaar 2 88% en 92%. Alle vrouwen stuurden de vragenlijst retour; er waren geen vroege of late complicaties van de behandeling. In deze kleine serie van gesteelde subsereuze vleesbomen die met UE zijn behandeld traden geen complicaties op. Onze bevindingen suggereren dat de behandeling van gesteelde vleesbomen met UE veilig en effectief is.

In hoofdstuk 8 hebben we retrospectief het voorkomen van infectie na UE bij 20 vrouwen met symptomatische vleesbomen en een aanwezig spiraaltje onderzocht. Voor en 3 maanden na UE werd een MR verricht en de UFS-QOL ingevuld. Na een gemiddeld vervolg van 21 maanden vulden de patiënten wederom de UFS-QOL in samen met een aanvullende vragenlijst over nadelige effecten en complicaties ten gevolge van infecties en ontstekingen. Een patiënte had, na 6 weken, een baarmoederverwijdering ondergaan ten gevolge van voortdurende pijn. Drie vrouwen hadden geringe klachten na de UE zonder dat medische behandeling nodig was. Bij geen van de patiënten heeft zich een infectie of ontsteking voorgedaan. De UFS-QOL scores verbeterden van 39 voor de behandeling tot 85 bij de laatste controle. We concludeerden dat de aanwezigheid van een spiraaltje niet als een contra-indicatie voor UE beschouwd moet worden.

In hoofdstuk 9 beschreven we de lange termijn klinische resultaten en de MR-bevindingen bij 71 vrouwen met een dominante vleesboom groter dan 10 cm of een baarmoedervolume van meer dan 700 cm³ die behandeld zijn met UE van augustus 2000 tot april 2005. Volume afname en infarcering van zowel de dominante vleesboom als de baarmoeder werd vastgesteld door de laatste MR te vergelijken met de MR van voor de behandeling. De symptomen van de patiënten werden op verschillende tijdstippen na de behandeling beoordeeld met behulp van gestandaardiseerde vragenlijsten. Er waren geen complicaties na behandeling. Gedurende een vervolgduur van gemiddeld 48 maanden hebben 10 van de 71 patiënten (14%) een verwijdering van de baarmoeder ondergaan. Gemiddeld nam het volume van de vleesboom met 44% en van de baarmoeder met 43% af. Gemiddeld was de infarcering van de vleesboom 86% en van de baarmoeder 87%. Bij de meerderheid van de patiënten was
er een substantiële afname van klachten. De klinische resultaten waren gelijk bij patiënten met een dominante vleesboom van meer dan 10 cm en bij patiënten met een grote baarmoeder op basis van meerdere kleine vleesbomen. Onze resultaten geven aan dat het risico op complicaties na UE bij deze vrouwen niet vergroot is. Bovendien zijn de klinische resultaten net zo goed als bij andere vrouwen die met UE behandeld worden. Derhalve moet een grote vleesboommassa niet als een contra-indicatie voor UE beschouwd worden.
Dankwoord

Het afronden van een promotie is een hele kluf. Het afronden van een promotie vanuit de perifere praktijk (en dan ook nog op licht gevorderde leeftijd) bleek een hele grote kluf. Deze promotie was nooit gelukt zonder de hulp en inspanning van velen.

Prof. dr. W.J.J. van Rooij, beste Willem Jan, promotor
“Nou, dan doen we dat toch”. Dat was je antwoord op de vraag of je wilde helpen met mijn promotie. En dat heb je ook altijd gedaan: ieder concept dat ik op Gmail zette, bleek de volgende ochtend al gecorrigeerd. Zonder je niet aflatend enthousiasme en geweldige drive hadden we hier vandaag niet gestaan.

Prof. dr. J.A. Reekers, beste Jim, promotor
Ook jij reageerde gelijk enthousiast op mijn mogelijke promotie en je hebt geweldig geholpen bij de afhandeling ervan.

Dr. P.N.M. Lohle en dr. P.F. Boekkooi, beste Paul en Focco, copromotoren
Dit proefschrift is eigenlijk het resultaat van het werk dat in 1998 gestart is door Harrie Vervest en Leo Lampmann en dat in de jaren erna door jullie geweldig is opgepakt. Samen hebben jullie het St. Elisabeth Ziekenhuis op de embolisatie-kaart gezet. Dat ik daar nu aan mee mag werken, beschouw ik als een voorrecht.

De leden van de leescommissie: Prof. dr. G.J. den Heeten, Prof. dr. M.J. Heineman, Prof. dr. H.A.M. Brölmann, Prof. dr. L.J. Schultze Kool, Prof. dr. M. Wieringa-de Waard en dr. O.M. van Delden wil ik dan ken voor het zitting nemen in de leescommissie en voor hun inspanningen.

Mijn overige maten: Klaas, Kees, Menno, Fiek, Gerlof en Jo
Een promotie gaat altijd over de rug van de maatschap. Deze promotie is daarop geen uitzondering. Jullie hebben daar nooit moeilijk over gedaan en waren altijd bereid dat ene stapje extra te zetten. Dank daarvoor. En Kees, wees gerust: even geen schetenwap meer!
Groskamp en Paul: paranimfen

Oude vriendschap roest niet.

De eerste ochtend van het werkkamp van “de eerste sociëteit der Nederlanden” in Noordwijk kwam je – geheel in legerkleding - uit je slaapzak en mepte de leiding de tent uit. Ik nam me voor een beetje uit je buurt te blijven. Dat is gelukkig niet gelukt.

Samen op de echo in het “Dijkzigt”; jij als oudste assistent, ik als jongste. Heerlijk zitten foeteren op alles en iedereen. Jammer dat het samenwerken tot de opleiding beperkt is gebleven.

En jij, je weet het zelf wel.
CURRICULUM VITAE

Albert Smeets is geboren in ’s-Gravenhage op 20 maart 1959. In 1977 begon hij aan de studie Geneeskunde aan de Universiteit van Leiden. In 1987 behaalde hij het arts examen en begon opleiding tot radioloog in het Erasmus Medisch Centrum in Rotterdam (opleider: prof. C. Hoornstra en later prof.dr. H.E. Schütte). Vanaf 1993 was hij verbonden als radioloog aan het Carolus-Liduina Ziekenhuis in ’s-Hertogenbosch. Vanaf 2001 is hij verbonden aan het St. Elisabeth Ziekenhuis in Tilburg. Sinds het pingpongen in 1973 is hij al 24 jaar getrouwd met Erica.