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Anu Ruuskanen

# *Uterine Artery Embolisation for Leiomyomas*

*Magnetic Resonance Imaging Studies and a Randomised Prospective Comparison with Hysterectomy*

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UNIVERSITY OF
EASTERN FINLAND

**ANU RUUSKANEN**

# *Uterine Artery Embolisation for Leiomyomas:*

## *Magnetic Resonance Imaging Studies and a Randomised Prospective Comparison with Hysterectomy*

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## ABSTRACT

Uterine leiomyomas constitute a substantial health issue for women and represent the most common single indication for hysterectomy. New treatment option, uterine artery embolisation (UAE) has been developed to substitute for major surgery but not evaluated in Finland.

The aim of this study was to compare the efficacy and safety of UAE and hysterectomy for the treatment of symptomatic leiomyomas in a prospective, randomised, controlled single-center trial with a 2-year follow-up. Further, magnetic resonance imaging (MRI) measures were used to assess the association of symptoms with MRI findings of leiomyomas, to evaluate the role of uterine ischaemia for the post-UAE pain, and to predict leiomyoma and uterus size reductions after UAE. Altogether 137 of 529 consecutive patients ready for hysterectomy were recruited to the study during 2002-2007 in Kuopio University Hospital in Finland. Twenty-seven patients were randomised to UAE and 30 to hysterectomy.

Analysed according to intention to treat, no major complications were encountered after UAE, while 7% of patients encountered major complications after hysterectomy. The mean hospitalisation and length of sick leave were shorter after UAE than after hysterectomy (1.3 vs 3.5 days, $P$=0.001; 11 vs 35 days, $P$=0.001; respectively). Menorrhagia relieved in 67% of UAE patients. Improvement of pressure symptoms was reported more frequently by UAE patients than by hysterectomy patients (95% vs 69%, $P$=0.029). Overall relief of symptoms (82% UAE vs 93% hysterectomy) and satisfaction of the treatments (89% UAE vs 97% hysterectomy) were good in both groups. Additional interventions were needed in 19% after UAE and in 10% after hysterectomy. Of preinterventional MRI characteristics, presence of a leiomyoma ≥50% protruding into uterine cavity, intense contrast enhancement of leiomyomas and smaller leiomyoma size were associated with menorrhagia. The large uterine and leiomyoma size were associated with increased urinary frequency, while urinary stress incontinence, abdominal pain, and pressure to back were not associated with any MRI finding. Myometrial ischaemia on 24-hour MRI and large volume of embolic material were associated with post-UAE pain that was often severe. Leiomyoma and uterus size reductions after UAE were predicted by leiomyoma-to-skeletal muscle T2 SI-ratio and T1-time of the pre-UAE MRI.

In summary, UAE is a safe and effective treatment for leiomyomas being preferable for patients with pressure symptoms. MRI findings of leiomyomata uteri give anatomical base for menorrhagia and increased urinary frequency. Post-UAE pain is partly explained by myometrial ischaemia. Uterus and leiomyoma size reduction after UAE can be predicted from pre-UAE MRI measures.

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Medical Subjects Headings: Hysterectomy; Leiomyoma; Magnetic resonance imaging; Microspheres; Prospective Studies; Randomized Controlled Trial; Treatment Outcome; Uterine Artery Embolization

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## TIIVISTELMÄ

Kohdun hyvänlaatuiset myoomat vaikuttavat potilaan elämänlaatuun aiheuttaessaan runsasta vuotoa (menorrhagia) ja lantion paineoireita. Ne ovat yleisin yksittäinen kohdunpoiston syy. Kirurgisen hoidon vaihtoehdoksi on kehitetty uusi hoito, kohtuvaltimoiden embolisaatio (UAE).

Tutkimuksen tarkoituksena oli selvittää UAE:n tehokkuutta ja turvallisuutta oireisten myoomapotilaiden hoidossa vertaamalla sitä kohdunpoistoleikkaukseen satunnaistetussa kahden vuoden seurantatutkimuksessa. Toisena tavoitteena oli arvioida magneettikuvauslöydösten (MRI) ja potilaan oireiden yhteyttä, UAE:n jälkeisen kivun liittymistä MRI-kuvassa näkyvään kohtulihaksen iskemiaan ja MRI-mittausten ennustavuutta kohdun ja myoomien koon pienenemiseen. Tutkimukseen rekrytoitiin vuosina 2002-2007 Kuopion yliopistollisen sairaalan naistentautipoliklinikalta peräkkäisiä naisia (137/529), joilla oli kohdunpoiston kriteerit täyttävä myoomatauti. Heistä 27 satunnaistettiin embolisaatioon ja 30 kohdunpoistoon.

Tuloksista ilmeni intention-to-treat –menetelmällä, että vakavia komplikaatioita ei esiintynyt emboloiduilla, mutta leikatuista niitä oli 7%:lla. Sairaalassaoloaika ja sairausloman pituus olivat lyhyemmät UAE:n jälkeen (1.3 vs 3.5 vrk, *P*=0.001; 11 vs 35 vrk, *P*=0.001). Kahden vuoden seuranta-aikana runsaat vuodot vähenivät 67%:lla emboloiduista. Paineoireet korjautuivat paremmin UAE:n jälkeen (95% vs 69%, *P*=0.029). Kokonaisuudessaan myoomiin liittyvien oireiden vähentymisessä ja tyytyväisyydessä hoitomuotoon ei ollut merkitsevää eroa (82% UAE vs 93% kohdunpoisto; 89% UAE vs 97% kohdunpoisto). Emboloiduista 19% ja leikatuista 10% tarvitsivat lisähoitoja seuranta-aikana. MRI-löydöksistä tilavuudestaan yli 50% kohtuonteloon työntyvä myooma, myoomien voimakas tehostuminen ja pienempi koko liittyivät menorrhagiaan ja myoomien suuri koko tihentyneeseen virtsaamistarpeeseen. Mikään MRI-löydöksistä ei liittynyt ponnistusinkontinenssiin, alavatsakipuihin tai selkään suuntautuviin paineoireisiin. Kohtulihaksen iskemia 24 tunnin MRI:ssä ja embolisaatiopartikkeleiden suuri määrä liittyivät kovaksi koettuun kipuun. Myoomien ja kohdun koon pieneneminen olivat yhteydessä myooman ja lihaskudoksen T2-signaalien suhteeseen ja T1-aikaan.

Tulokset osoittavat, että UAE on turvallinen hoitomuoto ja tehokas varsinkin paineoireista kärsiville myoomapotilaille. MRI-löydökset liittyvät menorrhagiaan ja tihentyneeseen virtsaamistarpeeseen. UAE:n jälkeinen kohtulihaksen iskemia selittää toimenpiteen jälkeistä kipua. MRI-mittauksilla voidaan ennustaa UAE:n jälkeistä kohdun ja myooman koon pienenemistä.

Luokitus: QZ 340, WN 185, WP 468
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Kuopio, March 2011

Anu Ruuskanen

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# *List of Original Publications*

The dissertation is based on the following original articles, which are referred to in the text by their Roman numerals:

**I** Ruuskanen A, Hippeläinen M, Sipola P, Manninen H. Association between magnetic resonance imaging findings of uterine leiomyomas and symptoms demanding treatment. Submitted.

**II** Ruuskanen A, Hippeläinen M, Sipola P, Manninen H. Uterine artery embolisation versus hysterectomy for leiomyomas: primary- and 2-year follow-up results of a randomised prospective clinical trial. European Radiology 2010;20:2524-32.

**III** Ruuskanen A, Sipola P, Hippeläinen M, Wüstefeld M, Manninen H. Pain after uterine fibroid embolisation is associated with the severity of myometrial ischaemia on magnetic resonance imaging. European Radiology 2009;19:2977-85.

**IV** Sipola P, Ruuskanen A, Yawu L, Husso M, Vanninen R, Hippeläinen M, Manninen H. Preinterventional quantitative magnetic resonance imaging predicts uterus and leiomyoma size reduction after uterine artery embolisation. Journal of Magnetic Resonance Imaging 2010;31:617-24.

# *Contents*

## ABBREVIATIONS

| | |
|---|---|
| CI | confidence interval |
| CIRSE | Cardiovascular and Interventional Radiological Society of Europe |
| DAP | dose-area-product |
| IR | inversion recovery |
| LNG-IUS | levonorgestrel releasing intrauterine system |
| MRI | magnetic resonance imaging |
| PACS | a picture archiving and communication system |
| PVA | polyvinyl alcohol |
| ROC | receiver operating characteristic |
| ROI | region of interest |
| SD | standard deviation |
| SF-36 | Medical Outcome Study Short Form 36 |
| SI | signal intensity |
| SIR | the Society of Interventional Radiology |
| TAGM | tris-acryl gelatine microspheres |
| TE | echo time |
| TR | repetition time |
| UAE | uterine artery embolisation |
| VRS | verbal rating scale |

# 1 Introduction

Uterine leiomyomas are the most common solid benign pelvic tumors in women during reproductive life (Wallach *et al.* 2004). An estimated 20-50% of leiomyomas are to produce symptoms (Buttram *et al.* 1981, Stovall 2001), such as prolonged or heavy menstrual bleeding (menorrhagia) and different pressure feelings in the pelvic area (Bukulmez *et al.* 2006). Menorrhagia may cause medical problems, but it also is a powerful source of social embarrassment and lost productivity for women at working life. Thus, leiomyomas have a major impact on quality of life and health (Pron *et al.* 2003a, Williams *et al.* 2006).

Surgical hysterectomy has been the standard treatment for leiomyomas, and symptomatic leiomyoma has been the single most common (in 2008, 39%) indication for hysterectomy in Finland (National Institute for Health and Welfare 2009, Brummer *et al.* 2009). As an alternative to surgery, uterine artery embolisation (UAE), by occluding the vascular supply of leiomyomas, has recently increasingly been applied worldwide (Goodwin *et al.* 2008, Tropeano *et al.* 2008). However, UAE is a rather novel treatment for leiomyoma patients and it has not been evaluated in Finland. Thus, it is important to investigate the effectiveness and safety of UAE, and patient satisfaction with this less invasive treatment.

There are several aspects associated with UAE not fully understood, indicating the need for a more thorough study. UAE can result in significant postprocedural pain as a primary adverse effect (Goodwin *et al.* 1999, Lampmann *et al.* 2007, Worthington-Kirsch *et al.* 1998) possibly reducing the satisfaction to the therapy. Furthermore, although the basic clinical rationale is that only symptomatic patients will be treated, it has not been scientifically evaluated which patients get the best benefit from UAE. Therefore, it would be very

useful if we could predict from preprocedural imaging findings which uterine leiomyomas will respond most favourably to UAE.

Transvaginal ultrasound imaging is used as a first imaging method to confirm the presence of leiomyomas. However, magnetic resonance imaging (MRI) has been suggested to be a highly accurate, noninvasive method for diagnosis of female pelvis pathology (Kirby *et al.* 2010, Murase *et al.* 1999). Although the typical MRI findings in patients with uterine leiomyomas are well established, the precise relationships between the size and location of uterine leiomyomas and their clinical implications are still unclear and results about associations between symptoms and leiomyoma MRI characteristics have been controversial (Gupta *et al.* 2008, Parker 2007, Viswanathan *et al.* 2007). Indeed, while various patient complaints are often attributed to leiomyomas, it is probable that not all pressure and pain symptoms are leiomyoma-related. Even the association between menorrhagia and leiomyomas is ambiguous. Therefore, establishment of the correct diagnosis is mandatory to avoid unnecessary therapeutic interventions and to inform the patient of likely treatment outcomes.

# 2 Review of the Literature

## 2.1 UTERINE LEIOMYOMAS

### 2.1.1 Etiology, Histopathology, and Epidemiology

Uterine leiomyomas are benign gynecological neoplasms of the uterus (Wallach *et al.* 2004). These tumors typically develop in women at fertile age, increase with age, and shrink after the menopause (Viswanathan *et al.* 2007), but hormone replacement therapy may even stimulate growth (Flake *et al.* 2003). Despite extensive research on the factors involved in the growth of leiomyomas, the precise causes of these tumors still remain unknown. Several predisposing factors have been identified, including age (late reproductive years), nulliparity, obesity, and African-American ethnicity (Flake *et al.* 2003). The growth of leiomyomas is ovarian hormones-dependent, i.e. estrogen and progesterone dependent. Actually these tumors contain estrogen and progesterone receptors (Zaloudek *et al.* 2002). Growth factors with mitogenic activity also are elevated in leiomyomas (Flake *et al.* 2003). Further, there is increasing evidence of genetic basis; previously mapped gene predisposes multiple leiomyomas and is related to familial leiomyomata (Tomlinson *et al.* 2002).

Histologically, leiomyomas are mesenchymal tumors and are easily identified as being of smooth muscle origin and benign, and they seem to be proliferation of a single clone of smooth muscle cell (Zaloudek *et al.* 2002). Leiomyomas can be located anywhere in the myometrium and are classified according to their location in the uterus: submucosal (projecting into the endometrial cavity and compressing the overlying endometrium), intramural (within the myometrium), and subserosal (beneath the serosa). Intramural location seems to be the most common. Submucosal leiomyomas can be pedunculated protruding to the uterine cavity, and subserosal

leiomyomas as pedunculated can lose its connection with uterus. Rarely, some become attached to another pelvic structure. Leiomyomas may be single or, more frequently, multiple. The size of uterine leiomyomas is variable, ranging from microscopic to extremely large tumors (Murase *et al.* 1999). Different degenerative changes are common in leiomyomas, hemorrhage and necrosis can be observed in leiomyomas, and some leiomyomas become extensively calcified (Zaloudek *et al.* 2002). Sarcomatous change of a previously benign leiomyoma to malign leiomyosarcoma is rare (Kitamura *et al.* 2005, Rha *et al.* 2003, Wallach *et al.* 2004).

Uterine leiomyomas are the most common pelvic gynecological tumors (Flake *et al.* 2003, Wallach *et al.* 2004), occurring with a remarkable frequency in more than 70% of reproductive age women (Cramer *et al.* 1990). Most uterine leiomyomas cause no symptoms (Buttram *et al.* 1981), and these tumors can be incidental (Zaloudek *et al.* 2002). However, leiomyomas have a major impact on the resources of health care, as they can cause significant morbidity (Brummer *et al.* 2009).

Although the phrase "uterine fibroid" is commonly used, for the purposes of clarify and scientific accuracy in this thesis, the colloquial term "fibroid" will not be used according to the standards of The Society of Interventional Radiology (SIR) (Hovsepian *et al.* 2009, Stokes *et al.2010*).

### 2.1.2 Symptoms

Most of women with uterine leiomyomas are asymptomatic. When symptomatic, leiomyomas may present with heavy prolonged menstrual bleeding (i.e. menorrhagia) (Stewart 2001), pain and a sensation of pressure or an uncomfortable feeling in pelvic area, increased urinary frequency, bloating, constipation, and rarely reproductive dysfunction (Buttram *et al.* 1981, Wallach *et al.* 2004). Menorrhagia may result in iron-defiency anaemia.

Although leiomyomas are common, the relationship between symptoms and leiomyomas is not clear. Results of previous studies are contradictory in assessing the association

between symptoms and MRI derived leiomyoma characteristics. Indeed, the factors that determine who get symptoms are unknown (Viswanathan *et al.* 2007). Studies imply that symptoms may depend on the location, size, and number of leiomyomas (Buttram *et al.* 1981). Submucosal leiomyomas may be more likely to cause menorrhagia (Stewart 2001), although large intramural leiomyomas that distort the endometrial cavity may also result in heavy bleeding (Clevenger-Hoeft *et al.* 1999). On the other hand, the cause of heavy bleeding in leiomyomata uterus without submucosal component is unresolved.

Large intramural and subserosal leiomyomas or large uteri with numerous leiomyomas may produce a pressure feeling to the adjacent organs, typically as located in the anterior part of uterus to the urinary bladder leading to increased urinary frequency and occasionally as located in the posterior part of the uterus to the bowel leading to constipation (Stewart 2001). An estimated 30% of women with uterine leiomyomas experience abdominal pain (Hutchins 1995), but the results about the association of the lower abdominal pain with leiomyomas have been controversial. Particularly hemorrhagic degeneration may be related with pain symptoms (Kawakami *et al.* 1994, Murase *et al.* 1999). In addition, acute pain can be caused by torsion of the pedicle of a pedunculated leiomyoma, or cervical dilatation by a submucosal leiomyoma protruding through the lower uterine segment (Wallach *et al.* 2004).

### 2.1.3 Clinical Evaluation

Leiomyomas are usually found incidentally in the gynecologic examination due to enlarged and deformed uterus. Bimanual palpation and estimation of the size of the uterus forms an important part of the examination. Transvaginal ultrasound performed by a gynecologist is the most readily available imaging technique and typically used to confirm the diagnosis and to exclude the possibility of other pelvic pathology. Transvaginal ultrasound should be used initially in clinical practice because it is the least invasive and most cost-effective tool (Evans *et al.* 2007). However, it may be inadequate

for determining the precise number and location of leiomyomas, particularly in the presence of large uteri. Three-dimensional or saline-infusion transvaginal ultrasound or hysteroscopy can be performed for confirming in case of uncertainty of sumucosal location.

Because the symptoms associated with leiomyomas can also be of other etiologies, it is mandatory that patients undergo adequate preprocedural evaluation. A Papanicolau test, and in the presence of significant bleeding symptoms, an endometrial biopsy should be performed and a recent blood count should be available.

### 2.1.4 Diagnostic Imaging

Although transvaginal ultrasound should be used initially in clinical practice because it is the least invasive and most cost-effective tool (Evans *et al.* 2007), MRI is an ideal tool for evaluating the characteristics of large uterine leiomyomas and especially leiomyoma location (Dueholm *et al.* 2002, Spielmann *et al.* 2006). Computed tomography is used sometimes due to poor availability of MRI. However, the high patient radiation dose decreases its usability in imaging leiomyomas. Further, advantages of MRI include increased spatial resolution and improved anatomic detail (Kirby *et al.* 2010).

## 2.2 MAGNETIC RESONANCE IMAGING OF LEIOMYOMAS

MRI, as a non-invasive tool, provides the most accurate assessment and excellent visualization of leiomyomas, as well as their size, location, and impact on adjacent structures (Dueholm *et al.* 2002, Dueholm *et al.* 2001, Hricak *et al.* 1986, Murase *et al.* 1999, Spielmann *et al.* 2006). Further, contrast-enhanced MRI before treatment can be used to determine the viability of leiomyomas and to detect other findings that would influence choosing the treatment (Nikolaidis *et al.* 2005). MRI can also be used to evaluate technical success of UAE and to image possible complications after UAE (Kirby *et al.* 2010).

*Appearance of Leiomyomas*

MRI of leiomyomas relies on T2-weighted fast spin echo sequences (Kirby *et al.* 2010). Nondegenerated uterine leiomyomas have a typical appearance on MRI: well-distinguishable and well-circumscribed tumors of homogenously decreased signal intensity (SI) compared with that of the myometrium in T2-weighted images (Hamlin *et al.* 1985, Hricak *et al.* 1986, Jha *et al.* 2000, Kido *et al.* 2003, Murase *et al.* 1999, Riccio *et al.* 1990) and considerable homogenous (cellular leiomyoma) enhancement equally to the myometrium on gadolinium enhanced sequences (Yamashita *et al.* 1993). On T1-weihted sequences, most leiomyomas are isointense to surrounding myometrium.

Gadolinium-enhanced MRI can distinguish nondegenerated leiomyomas from non-enhanced degenerated ones (Okizuka *et al.* 1993). Degenerated leiomyomas may show minimal and irregular enhancement and have variable appearances in T2-weighted images: higher SI and heterogeneous architecture (Yamashita *et al.* 1993). Further, leiomyomas with necrosis or with hyaline or calcific degeneration have low SI in T2-weighted images, while cystic degeneration shows high SI in T2-weighted images (Murase *et al.* 1999). Myxoid degeneration show very high SI in T2-weighted images and a minimal enhancement (Murase *et al.* 1999). Red degeneration (hemorrhagic infarction) may present with a variable signal pattern: periferal or diffuse high SI in T1-images and variable SI with a possible low-signal-intensity rim in T2-images (Kawakami *et al.* 1994). The signal characteristics of the rim can be explained as an effect of methemoglobin (Kawakami *et al.* 1994).

*Differential Diagnosis*

The differential diagnosis of leiomyomas on MRI includes adenomyosis, solid adnexal tumors, focal myometrial contraction, and uterine leiomyosarcoma (Murase *et al.* 1999).

Adenomyosis, as the diffuse form, appears as a thickening of the junctional zone (inner myometrium), whereas focal adenomyosis appears as a ill-defined low-signal-intensity mass

poorly marginated from the adjacent myometrium in T2-weighted images (Kido *et al.* 2003, Mark *et al.* 1987). In addition, bright spots are identified in T1- or T2-weighted images in adenomyosis (Kido *et al.* 2003).

Uterine myometrial contractions may simulate leiomyomas manifesting as a myometrial mass of low SI in T2-weighted images (Murase *et al.* 1999).

MRI findings that allow distinction between benign leiomyoma and malignant leiomyosarcoma are not fully established. Nevertheless, the infiltrative margins, rapid growth (Kido *et al.* 2003), or high SI within a uterine mass on T1-weighted and on T2-weighted images (Tanaka *et al.* 2004), or the invasion or metastatic spread may be indications of malignancy (Weinreb *et al.* 1990). Recently, the diffusion-weighted imaging has been evaluated in differentiating benign leiomyomas from sarcomas (Namimoto *et al.* 2009, Takeuchi *et al.* 2009). These results show that a combination of T2-weighted sequence and diffusion-weighted imaging improves sensitivity and specificity (Namimoto *et al.* 2009).

Further, MRI allows differentiation between pedunculated leiomyomas and adnexal masses due to the ability to demonstrate normal ovaries and the continuity or discontinuity of an adnexal mass with myometrium (Weinreb *et al.* 1990, Zawin *et al.* 1990).

## 2.3 TREATMENT OF LEIOMYOMAS

The aims of leiomyoma treatments are to reduce the symptoms considered to be related to leiomyomas; to reduce menstrual bleeding and pressure symptoms and pelvic pain, to correct the iron deficiency anaemia, and in selected cases, to improve fertility.

### 2.3.1 Hysterectomy and Myomectomy

Hysterectomy is the most common surgical treatment for leiomyomas for the women who have completed childbearing

(ACOG 2008). The main indication for hysterectomy in Finland is leiomyomas being 33-39% of all hysterectomies (2009, Brummer *et al.* 2009). The total number of hysterectomies on benign indications has decreased in Finland during years 2000-2008 from 10 000 to 7 000 (National Institute for Health and Welfare 2009, Brummer *et al.* 2009, Brummer *et al.* 2008) since a variety of new treatment approaches have become available (Tropeano *et al.* 2008). Indeed, as high as 50% of all hysterectomies was performed for leiomyomas two decades ago (Luoto *et al.* 1994a, Luoto *et al.* 1994b). Further, the Ministry of Social Affairs and Health in Finland has published the uniform criteria for non-emergency surgical hysterectomy for leiomyomas in 2005 (updated in 2010) (The Ministry of Social Affairs and Health 2010). According to these recommendations the hysterectomy is indicated if the score of 50 is gained: 50 points for leiomyoma over 10 cm in diameter or the greatest diameter of uterus over 20 cm; 30 points for submucosal leiomyoma, menorrhagia, a pressure feeling in pelvis, or urinary, defecation, or pain symptoms; and 20 points for the ineffective conservative treatments.

Laparoscopic and vaginal hysterectomies have become more common for benign indications comparing to abdominal route in Finland during recent years (Brummer *et al.* 2008) shortening the operation time, hospital stay, and sick leave (Brummer *et al.* 2009). Nevertheless, the hysterectomy is an invasive procedure with a risk of major complications (about 1% during years 2000-2005), such as urinary tract injury (ureteral or bladder injury), bowel injury, and hemorrhage (Brummer *et al.* 2008). Blood transfusions were given to 5 % of patients in the prospective nationwide FINHYST study (Brummer *et al.* 2009).

Myomectomy with various techniques is considered a treatment option for women who wish to preserve the possibility of pregnancy (Lumsden 2002). Abdominal myomectomy has been traditionally used. Laparoscopic myomectomy would be a treatment option for patients with subserosal or intramural leiomyomas, whereas submucosal leiomyomas can be removed by hysteroscopic myomectomy

(Lefebvre *et al.* 2003, Rovio *et al.* 2009). Vaginal myomectomy is achieved via colpotomy (Rovio *et al.* 2006). The proportion of myomectomies of leiomyoma treatments has been about 14% in Finland (National Institute for Health and Welfare 2009).

### 2.3.2 Uterine Artery Embolisation

UAE has been available from late 1970s, initially as a technique for postpartum and pelvic hemorrhage (Brown *et al.* 1979, Heaston *et al.* 1979, Pelage *et al.* 1998, Pelage *et al.* 1999a, Walker 1996, Walker *et al.* 1980). More recently, in 1995, it was reported for the treatment of symptomatic uterine leiomyomas (Ravina *et al.* 1995). The technique was used pre-surgery for limiting blood loss, but due to cessation of symptoms the surgery was cancelled. Since then, UAE has been under interest and research by interventional radiologists and gynecologists around the world. The greatest amount of data from the new technologies of the minimally invasive treatments for leiomyomas is of UAE (Sharp 2006). It has become increasingly available in treating leiomyomas, and currently approximately 25000 UAE procedures are now performed worldwide annually (Goodwin *et al.* 2008). However, in a recent study by Voogt et al. the authors found the marked variation in current practise of UAE in European countries (Voogt *et al.* 2010).

#### 2.3.2.1 Indications

SIR recommends that UAE be offered to only patients with uterine leiomyomas that are causing significant symptoms (heavy menstrual bleeding, pain, and bulk-related symptoms) (Andrews *et al.* 2009, Stokes *et al.* 2010). UAE represents a reasonable option especially for those who are at risk increased risk in the setting of surgery, or desire uterine preservation (Stokes *et al.* 2010).

#### 2.3.2.2 Contraindications

From the start, a viable pregnancy, active untreated gynecological infection, and gynecological malignancy have been considered absolute contraindications to UAE (Andrews *et*

*al.* 2009). Since then, SIR and Cardiovascular and Interventional Radiological Society of Europe (CIRSE) have aimed to unify these recommendations (Hovsepian *et al.* 2009, Stokes *et al.* 2010). Relative contraindications may be any conditions that may interfere with the normal healing response and place the patients at a higher risk of complications; immunocompromise, previous pelvic irradiation or surgery, chronic endometritis, coagulopathy, severe contrast material allergy, and renal impairment.

There are some leiomyoma locations or morphologic features that may make leiomyomas less ideal for embolisation, including narrow-based pedunculated or broad-ligament leiomyomas, and intracavitary leiomyomas (Kirby *et al.* 2010).

For patients with a history suggesting an underlying bleeding disorder that may be contributing to menstrual bleeding or may complicate percutaneus therapy, activated thromboplastin time and prothrombin time are recommened to be measured before UAE (Andrews *et al.* 2009).

At the time being, UAE is not recommended as a primary therapy for patients who desire to maintain fertility and childbearing potential; myomectomy seem to be an advisable treatment option for them (Goldberg *et al.* 2006, Usadi *et al.* 2007). Uncertainty about fertility after UAE has led to recent SIR guidelines that suggested that UAE is a relative contraindication for patients who wish to retain their fertility but may also represent the preferred alternative for patients who are not able to undergo a myomectomy (Hovsepian *et al.* 2009). The recent systematic literature review and meta-analysis of published studies identified altogether 227 completed pregnancies after UAE and the authors concluded that the risk of miscarriage seems to be increased after UAE (Homer *et al*. 2010). In contrast, one retrospective study found that UAE patients had better success rate than myomectomy recipients (Narayan *et al.* 2010). Uncomplicated pregnancies and normal deliveries after UAE have also been reported in other studies (Carpenter *et al.* 2005, Dutton *et al.* 2007, Goldberg *et al.* 2004, Holub *et al.* 2008, Kim *et al*. 2005, Mara *et al.* 2008, Pron *et al.* 2005, Walker *et al.* 2006a).

**2.3.2.3 Technique**

The goal of UAE is to deliver particulate emboli into both uterine arteries for the purpose of occluding or markedly reducing uterine flow at the arteriolar level, producing an irreversible ischaemic injury to the leiomyomas while avoiding permanent damage to the uterus (Marshburn *et al.* 2006, Stokes *et al.*, Tropeano *et al.* 2008).

***Technique***

The procedure is performed under fluoroscopic guidance under local anestesia and sometimes, if the patient demands, under conscious sedation. Percutaneus access is achieved through one or both femoral arteries; usually the unilateral approach is used via a right femoral artery. Some authors recommend routine aortography before embolisation with attention given to the presence of anomalious uterine arterial anatomy, especially possible supply from ovarian artery. However, a common practise is to perform aortography only in case that uterine artery anatomy is unusual (e.g. hypoplastic). Direct selective catheterization of both uterine arteries is performed with a 4 - or 5-French Cobra or Simmons shape catheter. In case of arterial spasm or difficult access selective catheterisation may require the use of micro-catheters and vasodilator agents to reduce the likelihood of technical failure. The catheter is placed approximately halfway along the uterine artery distally to the cervicovaginal branches, if possible. An arteriogram is obtained to visualize the anatomy of the arterial plexus supplying the leiomyoma. Then mixture of embolisation particles and contrast agent is slowly injected into the uterine artery during fluoroscopic monitoring carefully avoiding embolisation of ovaries through uterine-ovarian artery anastamoses and inadvertent reflux into other arterial branches. After the procedure, hemostasis at the puncture site is achieved by bimanual compression or by means of a vascular closure device.

***Medication***

Prophylactic antibiotics are routinely administered before and after embolisation to reduce the risk of infections (Goodwin *et al.* 2009). Administration of intravenous narcotics for often severe postprocedural pain and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are standard. Many analgesia protocols have been described for UAE, varying from NSAIDs and paracetamol to patient-controlled analgesia and to standard epidural anesthesia in some centers (Hehenkamp *et al.* 2006, Lampmann *et al.* 2007). An adequate and extensive pain management protocol for UAE is extremely important for the periprocedural and especially for the postprocedural period (Lampmann *et al.* 2007). UAE usually requires an overnight hospital stay for observation and intravenous pain medication.

***Angiographic Endpoint***

A number of angiographic endpoints have been used. Originally the technique of total occlusion, where embolisation particles are injected until flow in the uterine artery stops, was used. Recently, the limited embolisation, defined as a complete occlusion of branches to the peritumoral plexus and sluggish flow in the ascending segment of the uterine artery, leaving the main uterine artery, normal myometrial branches, cervicovaginal branches, and utero-ovarian anastomoses patent has become more popular (Joffre *et al.* 2004, Lohle *et al.* 2008, Pelage *et al.* 2003). This less aggressive embolisation of the uterine arteries may lead to the same clinical success rate, and reduced postprocedural pain and complications compared with complete embolisation (Pelage *et al.* 2003, Spies *et al.* 2001a).

The best method of achieving effective embolisation is still not evidence based. Even then, the technical success has been 88-99% in published studies (Joffre *et al.* 2004, Lohle *et al.* 2008, Pinto *et al.* 2003, Prollius *et al.* 2004, Pron *et al.* 2003b, Scheurig *et al.* 2006, Worthington-Kirsch *et al.* 2005). Variant anatomy of vessels seems to be the most common reason for failure to embolise bilaterally (Pron *et al.* 2003b, Volkers *et al.* 2006).

*Embolic Agents*

Several embolic agents have been available. UAE with calibrated tris-acryl gelatine microspheres (TAGM) (Laurent *et al.* 1996), polyvinyl alcohol (PVA) particles, gelatin sponge pledgets, and platinum coils have been reported (Joffre *et al.* 2004, Lohle *et al.* 2008, Scheurig-Muenkler *et al.* 2010, Spies *et al.* 2004a, Spies *et al.* 2007, Walker *et al.* 2002, Worthington-Kirsch *et al.* 2005).

One randomised study comparing PVA particles and TAGMs showed no differences in pain severity, in the frequency of incompletely infarcted leiomyomas, in the degree of improvement in symptoms score, or in patient satisfaction (Spies *et al.* 2004a). On the other hand, in other prospective randomised studies a significantly greater degree of leiomyoma infarction was obtained in patients embolised with microsphere particles than in those embolised with PVA particles (Siskin *et al.* 2008, Spies *et al.* 2005a). Actually, large (700-900μm) microsphere particles appear to penetrate significantly deeper into the leiomyoma compared with PVA particles (Chua *et al.* 2005). Further, spherical microsphere particles do not clump or aggregate leading to more controlled arterial occlusion and a precisely targeted tumor devascularization possibly with less extensive occlusion (Pelage *et al.* 2002).

Acrylamido PVA microspheres have also been shown to be an effective and safe embolic agent for UAE (Kroencke *et al.* 2008). This agent is in many ways similar to TAGMs (Worthington-Kirsch *et al.* 2010). One randomised study used acrylamido PVA microspheres instead of PVA particles to compare with TAGMs; no differences were found in perfusion scores of leiomyomas evaluated by 6-month MRI and in disease-specific symptom and health-related quality of life scores (Worthington-Kirsch *et al.* 2010).

Concerning the particle size, a prospective randomised study with 160 patients concluded that the use of PVA particles sizes 350-500μm was associated with higher pain scores compared to the use of particles sizes 500-700μm, but there was no differences in the decrease in size of leiomyoma, in the

leiomyoma ischaemia, or in the clinical outcome (Bilhim *et al.* 2011).

***Radiation Dose***

The uterus, ovaries, and urinary bladder are in the direct radiation beam and cannot be shielded in UAE. Further, the gonads are among the most radiation-sensitive organs in any individuals. Thus, to measure and document the fluoroscopy time, the number of images and the dose-area-product (DAP) for each individual UAE patient should be a standard practise in the interventional radiology.

Previous studies have reported mean fluoroscopic times between 14 and 36 minutes (Andrews *et al.* 2000, Glomset *et al.* 2006, Miller *et al.* 2003, Sapoval *et al.* 2010, Vetter *et al.* 2004). The mean DAP values has varied between 30 and 411 $Gycm^2$ depending on different techniques and equipments (Andrews *et al.* 2000, Glomset *et al.* 2006, Miller *et al.* 2003, Sapoval *et al.* 2010, Vetter *et al.* 2004).

Many factors may influence on the variation of patient doses, for example the difference of embolisation techniques, experience of the interventional radiologist, and the difference in patients' anatomy. It has been shown that the fluoroscopic time seems to correlate with the experience of the interventionist (Andrews *et al.* 2000, Pron *et al.* 2003c, Walker *et al.* 2002). Bratby et al. showed shorter fluoroscopic time when simultaneous embolisation of both uterine arteries was used with bilateral puncture of the groin (Bratby *et al.* 2007). Further, the use of pulsed fluoroscopy reduced ovarian dose significantly in two studies (Glomset *et al.* 2006, Nikolic *et al.* 2001). In addition, the use of low-dose and low-frame fluoroscopy and angiography (Sapoval *et al.* 2010) and the greater filtration (Glomset *et al.* 2006) allow a significant decrease in the patient dose. Thus, UAE requires the use of the highest-quality fluoroscopic equipment, and adequate training is essential for the performing physician (Spies *et al.* 2009a).

In one prospective study, where the procedures were performed by an experienced interventional radiologist in UAE,

the main component (about 50%) of the total DAP was the embolisation itself (White *et al.* 2007a). The same authors also showed that 20% of the total dose was related to the abdominal aortography. Aortography is usually performed to find the residual ovarian artery supply to the uterus after the completion of embolisation (Pelage *et al.* 2005). However, the utility of aortography in routine UAE is not clear, because of the small number of patients with substantial ovarian artery collateral supply and of the low sensitivity of aortography in the identification of this supply (White *et al.* 2007b). Preinterventional magnetic resonance angiography can help to predict ovarian artery supply of uterine leiomyomas while minimizing radiation exposure of conventional angiography during UAE (Kroencke *et al.* 2006).

**2.3.2.4 Treatment Outcome**

The initial clinical studies of UAE for leiomyomas were promising in short- and mid-term follow-up (Pelage *et al.* 2000, Ravina *et al.* 1995, Spies *et al.* 1999). In recent years many multicenter follow-up trials have been carried out (Goodwin *et al.* 2008, Myers *et al.* 2005, Pron *et al.* 2003a, Pron *et al.* 2003b, Pron *et al.* 2003c, Pron *et al.* 2005, Pron *et al.* 2003d, Pron *et al.* 2003e, Spies *et al.* 2007, Spies *et al.* 2005b, Walker *et al.* 2006b, Walker *et al.* 2002, Watson *et al.* 2002, Worthington-Kirsch *et al.* 2005).

The treatment seems to be well tolerated. Studies have suggested that recovery is rapid, a short hospital stay (1-3 days) (Bruno *et al.* 2004) and sick leave (1-2 weeks) are required in most cases (Pron *et al.* 2003d, Siskin *et al.* 2000, Walker *et al.* 2002, Worthington-Kirsch *et al.* 2005). Reports indicate that UAE appears to be effective in controlling the leiomyoma-related symptoms. The improvement of bleeding symptoms has been shown in 60-90% of patients and the relief of pressure and pain symptoms in 70-90% of women (Hirst *et al.* 2008, Joffre *et al.* 2004, Prollius *et al.* 2004, Pron *et al.* 2003c, Spies *et al.* 2005c). Patients' satisfaction with treatment seems to be high varying between 82-97% (Goodwin *et al.* 2008, Lohle *et al.* 2008, Prollius

*et al.* 2004, Spies *et al.* 2005b, Walker *et al.* 2002), and UAE appears to result in a durable improvement of quality of life (Goodwin *et al.* 2008, Spies *et al.* 2005c). On the other hand, quite large proportion of patients has been lost to follow-up.

The response of the leiomyomas in terms of decrease in size has been variable. However, remarkable reduction in the uterine and largest leiomyoma volumes have been demonstrated in follow-up ultrasound and MR imaging (Hirst *et al.* 2008, Joffre *et al.* 2004, Pinto *et al.* 2003, Prollius *et al.* 2004, Pron *et al.* 2003c, Scheurig *et al.* 2006, Spies *et al.* 2001b, Walker *et al.* 2002, Volkers *et al.* 2007). MRI seems to be useful follow-up technique after UAE to visualise outcome of treatment (Banovac *et al.* 2002, Burn *et al.* 2000, deSouza *et al.* 2002, Jha *et al.* 2000, Pelage *et al.* 2004). In particular, gadolinium enhanced MRI provides unique information for assessing the degree of infarction in the embolised leiomyomas after UAE (Katsumori *et al.* 2007, Katsumori *et al.* 2001).

Recent studies have shown that clinical failure may be associated with incomplete infarction of leiomyomas (Banovac *et al.* 2002, Pelage *et al.* 2004) as well as newly developed leiomyomas (Kim *et al.* 2010). Besides technical causes, additional ovarian artery supply of leiomyomas has been suggested as a cause of noninfarcted leiomyomas (Matson *et al.* 2000, Nikolic *et al.* 1999). Even with complete infarction of all leiomyomas, a viable uterus may give a rise to new leiomyomas. New leiomyomas growth was found in 20% of patients on MRI at 3-years follow-up (Pelage *et al.* 2004) and in 30% of patients at the mean follow-up of 5.8 years (Kim *et al.* 2010). Thus, evaluation with contrast-enhanced MRI is emerging as an essential part to assessing outcome of UAE (Spies 2009b). The need of additional intervention (hysterectomy, myomectomy, or repeat UAE) among patients in published studies has varied 8-28% in the long-term follow-up usually due to uncontrolled bleeding symptoms (Goodwin *et al.* 2008, Hirst *et al.* 2008, Narayan *et al.* 2010, Spies *et al.* 2005c, Spies *et al.* 2007, van der Kooij *et al* 2010.).

**2.3.2.5 Complications**

SIR and CIRSE have defined the complications on the basis of outcome (Stokes *et al.* 2010). Major complications result in admission to hospital for therapy, an unplanned increase in the level of care, prolonged hospitalisation, permanent adverse sequelae or death; minor complications result in no additional interventions and required no therapy or at most nominal therapy or overnight hospital stay for observation only.

The rate of complications has varied in individual studies perhaps due to different definitions of complications. The rate of minor complications has generally been around 5-20% and the rate of major complications at most a few percentages (Hirst *et al.* 2008, Spies *et al.* 2004b, Spies *et al.* 2002a, Worthington-Kirsch *et al.* 2005).

Complications of catheterization procedure itself include haematoma at the arterial puncture site, or vessel or femoral nerve injury (Hovsepian *et al.* 2009, Spies *et al.* 2002a); the procedural complication rate was 5% in Ontario trial (Pron *et al.* 2003b).

Expected general side effects of UAE have been estimated to appear in about 30% of UAEs (Hirst *et al.* 2008). Rather common primary adverse effect of UAE is significant postprocedural pain (Goodwin *et al.* 1999, Spies *et al.* 2002a, Worthington-Kirsch *et al.* 2005, Worthington-Kirsch *et al.* 1998) that may lead to longer hospital stay and hospital readmissions (Pron *et al.* 2003d). Treating this pain is essential but challenging (Lampmann *et al.* 2007). A few studies have evaluated postprocedural pain and pain management (Hehenkamp *et al.* 2006, Pron *et al.* 2003d, Siskin *et al.* 2002, Worthington-Kirsch *et al.* 1998), but the specific cause of the pain is not fully understood. However, the data imply that leiomyoma ischaemia and transient uterine ischaemia, in particular, could be responsible for the immediate postprocedural pain (Banovac *et al.* 2002, Burbank 2004, Burbank *et al.* 2000, Pelage *et al.* 2000, Ryu *et al.* 2003, Siddiqi *et al.* 2006). This pain is expected for several hours after embolisation and is not considered a complication unless unplanned medical therapy, prolonged hospitalisation, or

unexpected admission to the hospital is needed (Hovsepian *et al.* 2009, Stokes *et al.* 2010).

Postembolisation syndrome also is an expected aspect of recovery and should not be considered a complication by the same token (Hovsepian *et al.* 2009, Stokes *et al* 2010.). It is composed of pelvic pain, low-grade fever, nausea, vomiting, loss of appetite, and malaise in the first few days after undergoing UAE.

Natural expulsion of the whole or parts of the infarcted leiomyomas has not been classified as complication (Burbank 2008). Further, vaginal discharge after UAE may occure. But then, if infarcted and necrotic leiomyoma tissue is exposed to the uterine cavity, there is risk of infectious complications (Burbank 2008, Verma *et al.* 2008). There are infrequent reports as individual cases of uterine infection, pyomyoma, endometritis, and uterine necrosis (Spies *et al.* 2002a) possibly leading to an emergent hysterectomy. The routine use of antibiotics varies in clinics (Marshburn *et al.* 2006). According to the HOPEFUL study prophylactic antibiotics seems to protect against complications and side effects (Hirst *et al.* 2008).

Irregular menses, transient or permanent amenorrhea due to ovarian failure have been reported after UAE (Spies *et al.* 2005b, Walker *et al.* 2002). It is possible for embolic agents to enter in the ovarian vessels through collateral circulation with a decrease in ovarians blood supply (Pelage *et al.* 1999b, Ryu *et al.* 2001) leading to transient amenorrhea (12-28%) (Goodwin *et al.* 2008, Lohle *et al.* 2008, Spies *et al.* 2005c, Spies *et al.* 2004b, Spies *et al.* 2007). In a study by Chrisman et al. 15% of patients encountered secondary amenorrhea, however, the premature ovarian failure is rare among patients younger than 45 years (Chrisman *et al.* 2000, Lohle *et al.* 2008, van der Kooij *et al.* 2010).

Major or potentially fatal complications occur very infrequently; deep vein thrombosis, pulmonary embolus, arterial thrombosis, nontargeted embolisation, urinary tract infection, urinary retention, septicaemia, death, tubo-ovarian abscess, or inadvertent embolisation of leiomyosarcoma being reported (Hovsepian *et al.* 2009, Spies *et al.* 2002a).

### 2.3.3 Other Uterus Sparing Treatments

There are a number of other new mini-invasive options for the treatment of uterine leiomyomas. The magnetic resonance-guided high intensity focused ultrasound (HIFU) ablation is a hybrid technique using the heat-generating ability of ultrasound combined with MRI, which provides anatomical guidance, the real-time thermal monitoring, and postprocedural assessment of the treatment extent (Al Hilli *et al.* 2010, Cowan *et al.* 2002, Hesley *et al.* 2008).

Different techniques of myolysis via the laparoscopic or hysteroscopic route have been demonstrated. Under ultrasound monitoring, the fibers connected with laser energy are inserted into the leiomyoma by laparoscopy in interstitial coagulation (Visvanathan *et al.* 2002), while cryomyolysis is performed by destroying leiomyoma tissue with cryoprobe (Zupi *et al.* 2004).

The percutaneus approach is used in MRI guided thermo-ablation with laser fibers (Law *et al.* 2000) or in MRI guided cryotherapy (Cowan *et al.* 2002).

Rather than embolising uterine arteries Hald et al. demonstrated laparoscopic uterine artery occlusion where uterine arteries are closed with the endoclips (Hald *et al.* 2007, Hald *et al.* 2004, Hald *et al.* 2009). Transvaginal Doppler-guided uterine artery occlusion with a device containing a vascular clamp has also been developed (Brill 2009).

Hormonal therapy is used to relieve symptoms associated with uterine leiomyomas. Gonadotropin-releasing hormone analogues/agonists (GnRHa) were thought to produce a hypoestrogenic effect in various estrogen-dependent conditions, e.g. uterine leiomyomas, by inhibiting gonadotropin secretion and suppressing ovarian function (Wallach *et al.* 2004). These compounds have been reported to have an influence on leiomyoma growth; the shrinkage of leiomyomas, decreasing the uterine volume, and diminishing patient symptoms (Fiscella *et al.* 2006, Wallach *et al.* 2004). However, the effect of GnRHa treatment is transient, and after discontinuing administration, leiomyomas tend to return to their pretherapeutic size, and symptoms commonly return (Wallach *et al.* 2004). Some

important side effects of hormonal therapy have been reported; menopause, postmenopausal symptoms and osteoporosis.

### 2.3.4 Comparison of UAE with Other Treatments

Outcomes of comparative randomised trials of UAE and hysterectomy and of comparative non-randomised multicenter studies are summarized in **Table 1**.

Thus far, three randomised trials comparing UAE and hysterectomy have been carried out: a Spanish singlecenter trial by Pinto et al. (Pinto *et al.* 2003) with 60 randomised patients and a 6-month follow-up, a multicenter REST trial in the UK with 157 randomised patients and a 12-month follow-up (Edwards *et al.* 2007), and a multicenter EMMY trial in the Netherlands with 177 randomised patients and a 5-year follow-up (Hehenkamp *et al.* 2006, Hehenkamp *et al.* 2008, Hehenkamp *et al.* 2005, van der Kooij *et al.* 2010, Volkers *et al.* 2007, Volkers *et al.* 2006, Volkers *et al.* 2008a).

The primary outcomes in the randomised trials have been as follows: REST trial, quality of life (Edwards *et al.* 2007); Pinto et al., the length of hospital stay (Pinto *et al.* 2003); and EMMY trial, clinical success with regard to if UAE could avoid a hysterectomy in at least 75% of cases (Volkers *et al.* 2007). In addition, a retrospective multicenter cohort study (HOPEFUL) compared the safety and efficacy of UAE and hysterectomy (Dutton *et al.* 2007, Hirst *et al.* 2008). One prospective observational multicenter study compared the clinical outcome of UAE and hysterectomy (Spies *et al.* 2004b).

In published studies patients in the UAE group seemed to recover faster than patients in the hysterectomy group (Edwards *et al.* 2007, Hehenkamp *et al.* 2006, Pinto *et al.* 2003, Spies *et al.* 2004b). The major complication rate has been significantly higher after hysterectomy than after UAE in two studies (Dutton *et al.* 2007, Pinto *et al.* 2003), whereas REST and EMMY trials reported no differences in major complication rate, but more minor complications after UAE (Edwards *et al.* 2007, Hehenkamp *et al.* 2005). On the other hand, a definition of minor

*Table 1*

*Comparative trials [a] between UAE and hysterectomy*

| Study, year | Study type | No. of patients | Follow-up | Complications (%) | Improvement of symptoms (%) | | | Hysterectomy after UAE (%) | Satisfaction (%) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Menorrhagia after UAE | Pressure symptoms | Overall symptoms | | |
| Pinto et al. 2003 | RCT single center | 57; UAE 38, hys 19 | 6 mo | total 25 vs 20, major 0 vs 25 | 86 | NA | NA | 5 | 86 vs 88 [c] |
| Hehenkamp, Volkers, van der Kooij et al. 2005-2010 (EMMY) | RCT multicenter 28 centers, | 156; UAE 81, hys 75 | 2 yrs and 5 yrs | minor 58 vs 40, major 5 vs 3 | at 2yrs 96; at 5 yrs 83 | at 2 yrs 66 vs 69 at 5 yrs UAE better | NA | at 2yrs 23; at 5yrs 28 | at 2 yrs 91 vs 88; at 5yrs 85 vs 89 [d] |
| Edwards et al. 2007 (REST) | RCT multicenter, 27 centers | 157; UAE 106, hys 43, myom 8 | 12 mo | minor 34 vs 20, major 15 vs 20 | NA | NA | 3.6 vs 4.3 [e] | 6 | 88 vs 93 [b] |
| Dutton et al. 2007, Hirst et al. 2008 (HOPEFUL) | retrospective multicenter, 18 centers | 1108; UAE 649, hys 459 | UAE 4,6 yrs; hys 8,6 yrs | minor 15 vs 14, major 4 vs 11 | 64 | Urinary function worse after hys. | 80 vs 89 | 11 | 87 vs 70 [b] 80 vs 70 [c] |
| Spies et al. 2004b | prospective multicenter, 11 centers | 152; UAE 102, hys 50 | 12 mo | total 28 vs 50, major 4 vs 12 | 61% score reduction | 83 vs 95 | No difference. | NA | 90 vs 97 [d] |
| Ruuskanen et al. 2010 | RCT single center | 57; UAE 27, hys 30 | 2 yrs | major 0 vs 7 | 67 | 95 vs 69 | 82 vs 93 | 12 | 89 vs 97 [c] |

The outcome results are UAE versus (vs) hysterectomy unless otherwise specified. UAE, uterine artery embolisation. Hys, hysterectomy. NA, not available.

[a] Randomised controlled trials and largest comparative non-randomised trials between UAE and hysterectomy.

[b] Patients would recommend the treatment to a friend.

[c] Patients would choose the treatment again.

[d] Patients were moderately or very satisfied with the symptom outcome.

[e] Symptom scores (numbers are mean) range from -5 (markedly worse) to +5 (markedly better).

complication has varied in different studies making the comparison of results difficult.

Results of improvement of pressure and pain symptoms have been controversial (Spies *et al.* 2004, Volkers *et al.* 2007). In two studies the improvement of symptom scores (Edwards *et al.* 2007) and of general health (Hirst *et al.* 2008) were significantly better after hysterectomy than after UAE. On the other hand, EMMY trial showed no difference in increase in quality of life after the treatments (van der Kooij *et al.* 2010). However, to compare the results of general health and quality of life is difficult due to different ways to perform the measurements in the studies.

Total costs were significantly lower for UAE than for hysterectomy in two randomised trials (Edwards *et al.* 2007, Volkers *et al.* 2008a). HOPEFUL study also indicated that UAE is less expensive than hysterectomy even after further treatments for unresolved or recurrent symptoms are taken into account (Wu *et al.* 2007).

Similarly to UAE, myomectomy is not a definitive treatment either. Mara et al. compared UAE and myomectomy in a randomised controlled trial and found that there were no differences in the technical or clinical success, or in the complication rate, or in the number of reinterventions, but the embolised patients underwent a shorter hospital stay and recovery period (Mara *et al.* 2008).

Laparoscopic occlusion of uterine arteries also has been compared to UAE in a randomised study that demonstrated better improvement in bleeding symptoms after UAE than after laparoscopic occlusion (Hald *et al.* 2007, Hald *et al.* 2009). On the other hand, in another randomised trial UAE and laparoscopic occlusion were comparable with regard to symptom relief (Ambat *et al.* 2009).

# *3 Aims of the Study*

The general aim of the study was to compare UAE in treating symptomatic leiomyoma patients with hysterectomy and to evaluate pre- and post-UAE MRI findings of leiomyomas.

The more specific aims were:

**I**: To investigate the association between MRI derived characteristics of uterine leiomyomas and treatment-worthy symptoms; menorrhagia, and pressure and pain symptoms.

**II**: To prospectively compare UAE and hysterectomy for the treatment of symptomatic leiomyomas, particularly the clinical success at 2-year follow-up, in a randomised controlled trial.

**III**: To evaluate the frequency and extent of uterine ischaemia after UAE using MRI and to study the role of myometrial and leiomyoma ischaemia in the pathogenesis of postprocedural pain.

**IV**: To investigate the relationship between pre-UAE MRI measures and uterus and leiomyoma size reductions after UAE.

# 4 Patients and Methods

## 4.1 STUDY DESIGN AND PATIENTS

The study protocol was approved by the Ethics Committee of Kuopio University Hospital and written informed consent was obtained from participating patients.

**Figure 1** illustrates patient flow in the recruitment and during the randomised study. During the recruitment period (between 2002 and 2007) altogether 529 women were referred to the gynecology outpatient clinic of Kuopio University Hospital due to symptomatic leiomyomas that demand treatment. One hundred thirty-seven of them were eligible and were recruited to the prospective study to undergo either UAE or hysterectomy. Fifty-seven patients of participants were randomised. The rest 80 patients who refused to be randomised were prospectively followed up as the randomised ones. Finally, UAE was performed altogether for 86 patients (26 randomised and 60 prospectively followed up only).

A flow diagram of clinical and MRI follow-up protocol is shown in **Figure 2**. **Table 2** demonstrates the study design and patient flow for Studies I-IV. Those patients whose preprocedural MRI was available were included in Study I. Those patients who were treated with UAE and whose MRI examinations were available were included in Studies III and IV.

Inclusion and exclusion criteria to the study are shown in **Table 3**. Symptoms had to be severe enough to warrant consideration of hysterectomy.

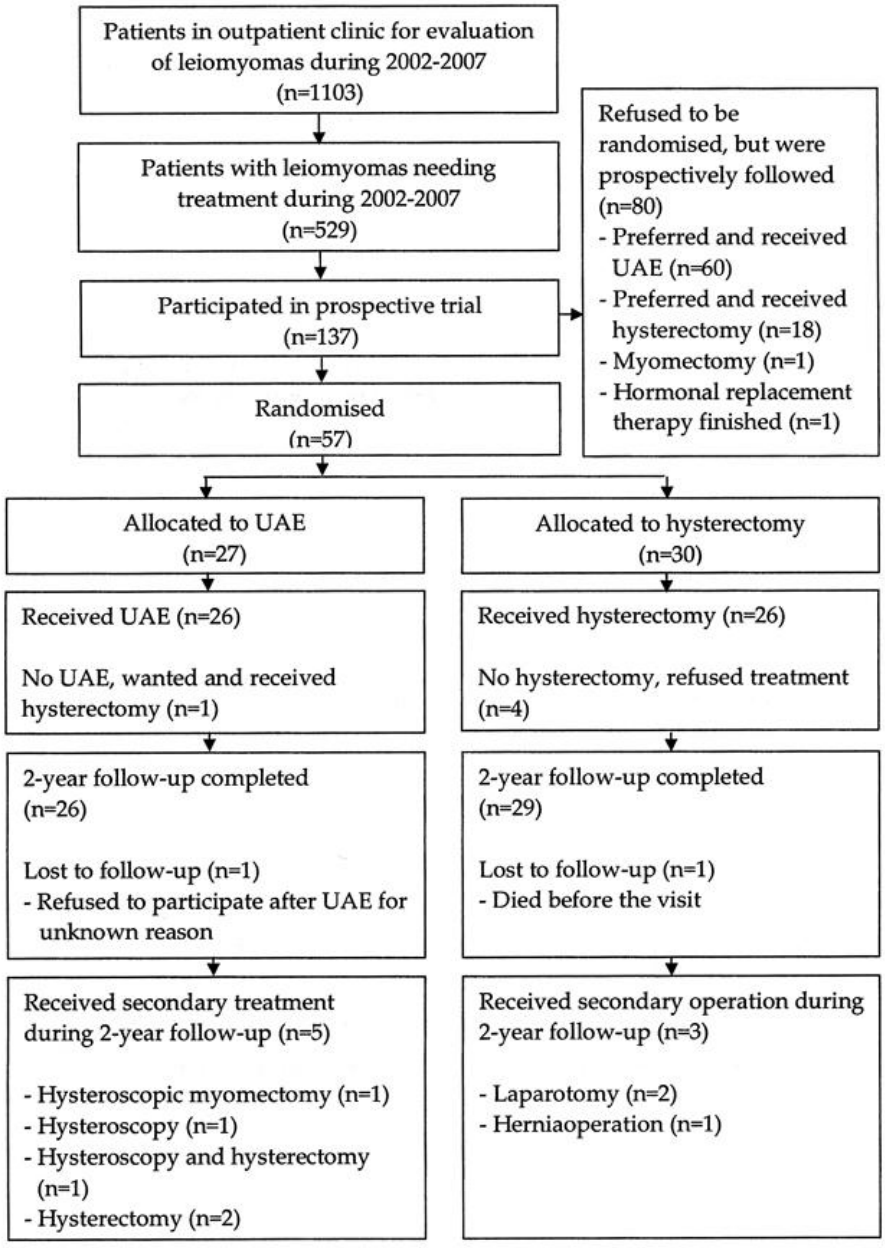


***Figure 1***
*Patient flow in the recruitment and during the randomised study.*

***Table 2***

*The study design*

| Study | Study purpose | Patients (n) | Methods |
|---|---|---|---|
| Study I | To evaluate the association of symptoms with MRI findings | 122 | Symptom questionnaire, preprocedural MRI |
| Study II | To compare the clinical success of UAE and hysterectomy for the treatment of leiomyomas | 57;<br>27 to UAE,<br>30 to hys | Randomised comparison by intention to treat in 2-year follow-up |
| Study III | To evaluate the role of myometrial and leiomyoma ischaemia in postprocedural pain after UAE using MRI | 62 | UAE,<br>Preprocedural MRI,<br>24-hour follow-up MRI |
| Study IV | To investigate the value of preprocedural MRI measures in predicting uterus and leiomyoma size reduction after UAE | 52 | UAE,<br>Preprocedural MRI,<br>6-month follow-up MRI |

UAE, uterine artery embolisation. Hys, hysterectomy. MRI, magnetic resonance imaging.

***Table 3***

*Inclusion and exclusion criteria to the prospective study*

| Inclusion criteria | Exclusion criteria |
|---|---|
| - treatment-requiring symptoms [a] | - suspected genital tract malignancy |
| - imaging confirmed leiomyomas | - adnexal pathological features |
| - agreeing to hysterectomy, if necessary | - acute pelvic inflammatory disease |
| | - viable pregnancy or fertility preservation |
| | - uterovaginal prolapse requiring treatment |
| | - incontinence requiring treatment |
| | - leiomyoma suitable for hysteroscopic myomectomy [b] |
| | - renal impairment |
| | - previous reactions to contrast media |
| | - endometriosis requiring treatment [c] |
| | - clinically suspected adenomyosis [c] |

[a] Symptoms had to be severe enough to warrant consideration of hysterectomy.
[b] A single leiomyoma 5cm or less in size and with ≥50% protrusion into the uterine cavity.
[c] Relative contraindications.

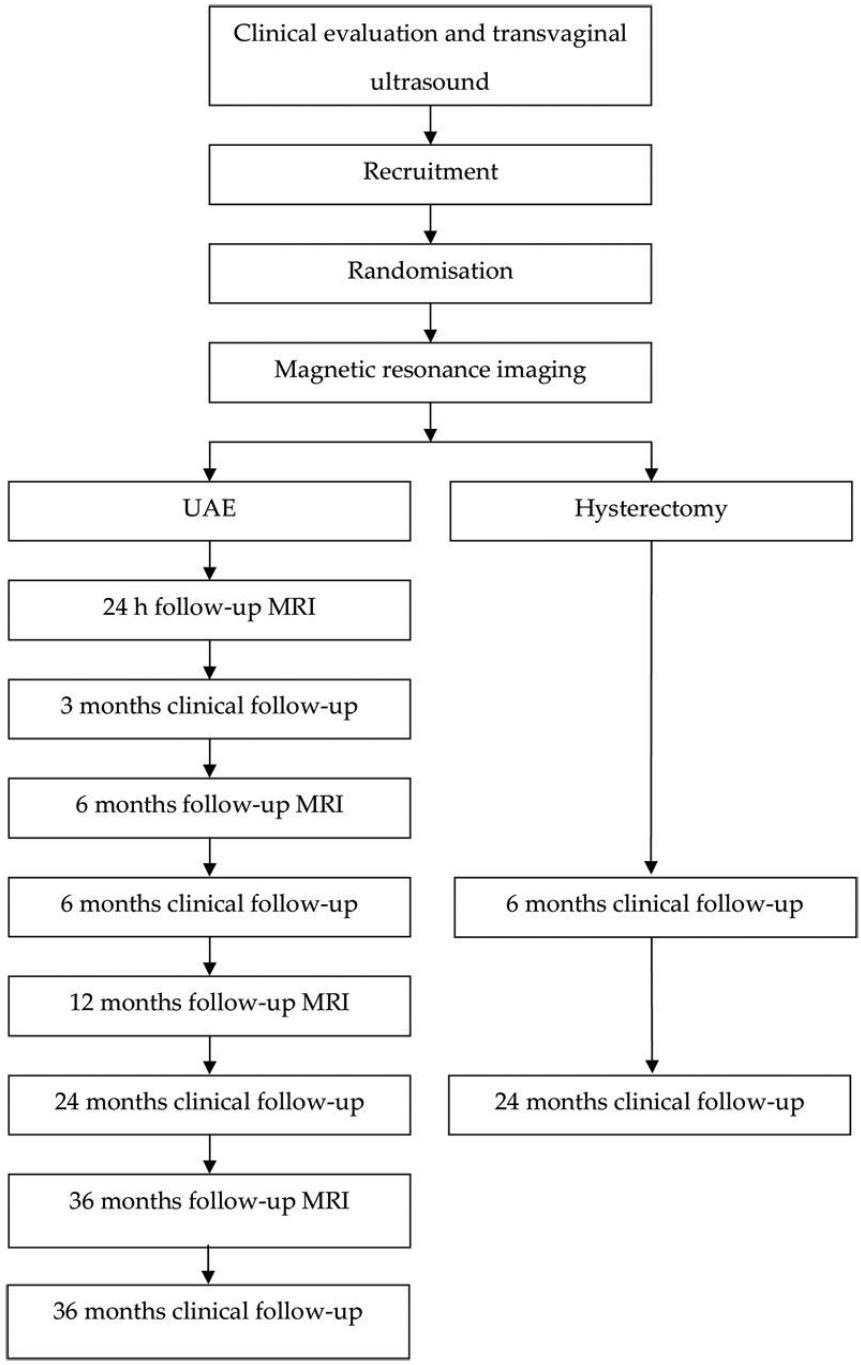


***Figure 2***

*A flow diagram of clinical and magnetic resonance imaging follow-up.*

## 4.2 SYMPTOMS AND CLINICAL EVALUATION

The initial prospective evaluation of the patients included medical and gynecological history and examination by a gynecologist, who interviewed the patients using a questionnaire. The asked symptoms and their classification are shown in **Table 4**. Transvaginal ultrasound, Pap smear and endometrial sampling were performed. Complete blood count, ferritin, haematocrit, follicle-stimulating hormone, and oestrogen levels were determined.

For analyses, patients in Study I were divided into three groups according to the symptoms reported: 1) patients with menorrhagia alone; 2) patients with pressure symptoms alone; and 3) patients with both menorrhagia and pressure symptoms.

***Table 4***

*Structured questionnaire for registering the symptoms*

| **Symptom** | **Classification** | | | |
|---|---|---|---|---|
| Menstrual flow | | | | |
| Duration | in days | | | |
| Severity[a] | no periods | mild | moderate | severe[b] |
| The frequency of changing sanitary protection | normal | increased[c] | | |
| A pressure feeling [d] | none | mild | moderate | severe |
| To the bladder | none | mild | moderate | severe |
| To the bowel | none | mild | moderate | severe |
| To the back | none | mild | moderate | severe |
| Increased urinary frequency [d] | none | mild | moderate | severe |
| Urinary stress incontinence [d] | none | mild | moderate | severe |
| Pain [d] | | | | |
| Dysmenorrhea | none | mild | moderate | severe |
| Non-menstrual related lower abdominal pain | none | mild | moderate | severe |

[a] Moderate or severe indicates 'menorrhagia'.
[b] Menstrual flow was defined as 'severe' when it prevented participation in everyday activities, caused anemia, and extra large pads and/or tampons were needed.
[c] Change was required at 1- to 2-hour intervals and both pads and tampons were needed at night.
[d] Mild, moderate and severe indicates 'yes'.

## 4.3 MAGNETIC RESONANCE IMAGING

### 4.3.1 MRI Protocol

All MRI studies were performed with an identical protocol at 1.5 T (Siemens Vision; Siemens Medical System, Erlangen, Germany) using a phased-array body coil.

*Imaging Technique for Anatomical Imaging (Studies I, II, III and IV)*

Transverse and sagittal T2-weighted turbo SE imaging (TR/TE 3,600/138 [repetition time msec/echo time msec]; flip angle 180°; echo train length 29; in-plane matrix 116×256; field of view 350 cm; section thickness 6 mm; intersectional gap 1.5 mm) without contrast agent, and transverse and sagittal T1-weighted gradient-echo imaging (TR/TE 170/2.3; flip angle 70°; in-plane matrix 172 × 256; field of view 300 cm; section thickness 6 mm without intersectional gap) before and after contrast agent injection were performed. Gadobutrol (Gadovist; Schering, Berlin, Germany) was administered at 0.1 mmol/kg of body weight. The injection was performed at 5 mL/s. Non-dynamic imaging was initiated 1.5 minutes after contrast agent injection.

*Imaging Technique to Obtain the T1 Relaxation Time (Study IV)*

To obtain T1 relaxation time one slice at the mid-level of the dominant leiomyoma (defined as a leiomyoma with largest diameter) was imaged with inversion recovery (IR) pulse sequences (TR/TE 7.7/4.2; flip angle 15°; in-plane matrix 128 × 128; slice thickness 8 mm). Imaging was repeated 10 times with variable inversion times (10, 100, 200, 300, 400, 500, 800, 1600, 3200, and 5000 msec).

### 4.3.2 MRI Analysis

All analyses were performed using the picture archiving and communication system (PACS) with IDS5-software (Sectra, Linköping, Sweden).

#### 4.3.2.1 Anatomical Analysis (Studies I, II, III and IV)

The number and volume of leiomyomas and uterine diameters were determined from transverse and sagittal T2-weighted images. A leiomyoma was defined as a clearly distinguishable and well-circumscribed tumor of homogenously decreased or variable heterogeneous SI compared with that of the myometrium in T2-weighted images, depending on the type of degeneration (Murase *et al.* 1999). Leiomyoma diameters were measured in three planes and the volume was calculated using the formula for a prolate ellipse. For each patient, the total volume of all leiomyomas was calculated by summing the individual leiomyoma volumes. The uterine diameters were measured in three planes: the length and anteroposterior diameters from sagittal images, and the transverse diameter (width) from axial images.

The volume of the uterus was measured using sequential transverse contrast-enhanced T1-weighted images. The borders of the uterus were delineated, and the volume was calculated by summing the area measurements of individual slices and multiplying the summed areas by the slice thickness. This resulted in a true three-dimensional volume of the uterus. The volume of the uterine corpus was measured in the same manner by excluding the cervix (Study III). The volume of the myometrium was calculated by subtracting the volume of the leiomyomas from the volume of the uterine corpus (Study III).

The other anatomical characteristics of leiomyomas and uteri were determined from transverse and sagittal T2-weighted images. Leiomyoma location was designated as the location of the center of the leiomyoma. The submucosal leiomyomas were classified according to the proportion of leiomyoma protruding into the uterine cavity according to the European Society of Gynecological Endoscopy Classification of Submucous Fibroids (Wamsteker *et al.* 1993). Thus, the relationship of leiomyomas to the uterine endometrium was classified into four categories: 1) presence of submucosal leiomyoma largely (≥50%) protruding into the uterine cavity (also including the pedunculated submucosal leiomyomas); 2) presence of a leiomyoma <50%

protruding into the uterine cavity (i.e. intramural leiomyoma with minor submucosal component); 3) intramural or subserosal leiomyomas only in contact with the junctional zone; or 4) intramural or subserosal leiomyomas without contact with the junctional zone. These categories are illustrated in **Figure 3**. The junctional zone was defined as a hypointense ring beneath the endometrium in T2-weighted images.

One radiologist performed the preinterventional MRI analyses (Studies I, II, III). In Study IV assessment of volumes of dominant leiomyomas and uteri from both pre- and follow-up MRIs were performed by two radiologists.

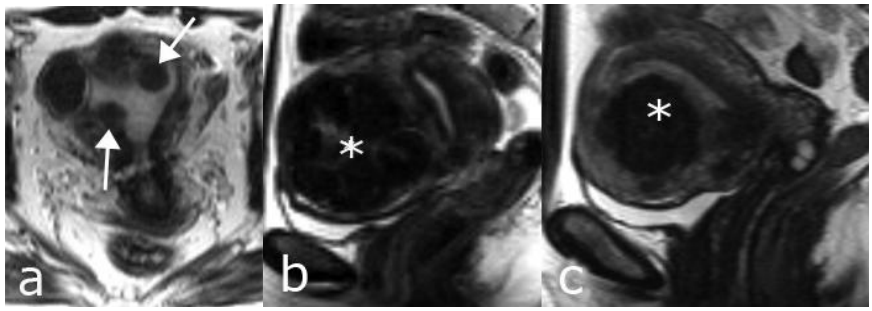


***Figure 3***

*Characterization of leiomyoma/endometrium relationship. Preprocedural non-enhanced T2-weighted turbo spin echo MR images from three patients. (a) In a transverse image obtained from the patient with menorrhagia two small submucosal leiomyomas (arrows) largely (≥50%) protrude into the uterine cavity. (b) A sagittal image obtained from the patient with increased urinary frequency shows an intramural leiomyoma (asterisk) without contact in the junctional zone. (c) A sagittal image obtained from the patient with a pressure feeling on the bladder and mild menstrual flow shows a leiomyoma (asterisk) protruding into the uterine cavity indicating minor (<50%) submucosal component.*

#### 4.3.2.2 Tissue Characterization Analysis (Studies I, III, and IV)

***Enhancement and Degeneration of Leiomyomas on Preprocedural MRI (Study I)***

The percentage of enhanced tissue of all leiomyomas was assessed visually from contrast-enhanced T1-weighted images as shown in **Figure 4**. The presence of hemorrhagic degeneration as a possible cause of abdominal pain was registered. Hemorrhagic degeneration shows a peripheral or diffuse high SI on T1-weighted images and variable SI with a possible low SI rim on T2-weighted images (Kawakami *et al.* 1994, Murase *et al.* 1999).

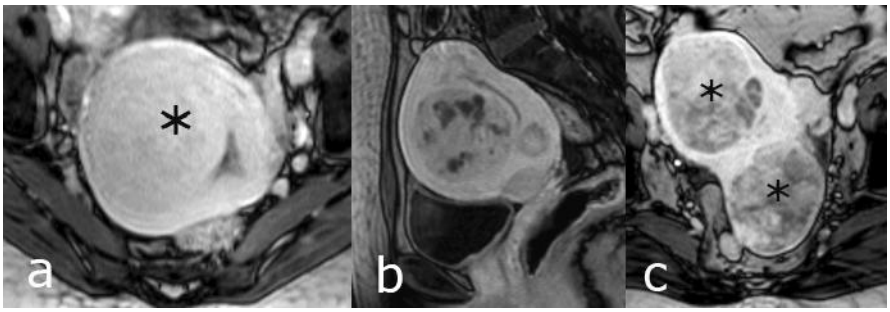


***Figure 4***

*Assessment of enhancement of leiomyomas. Enhanced T1-weighted gradient-echo MR images illustrate the enhancement of leiomyomas in three patients. A transverse (a) image shows intense (100%) enhancement of the large single leiomyoma (asterisk), a sagittal (b) image shows 80% enhancement of leiomyomas, and a transverse (c) image 30% enhancement of large leiomyomas (asterisks).*

***Twenty-four Hour Postprocedural MRI Analysis: Myometrial and Leiomyoma Ischaemia (Study III)***

Contrast enhancement of leiomyomas and myometrium was assessed visually from transverse and sagittal contrast enhanced T1-weighted images. The presence of nonenhancing tissue (i.e. ischaemic) was registered. First, the percentage of ischaemic tissue in the dominant leiomyoma, in all leiomyomas, and in myometrial tissue of the uterine corpus was estimated. In the semi-quantitative analysis, the absolute volumes of ischaemic

tissue (ml) in the myometrium, in the dominant leiomyoma, and in all leiomyomas were calculated. Second, the severity of myometrial ischaemia was graded into four categories: grade 1, no ischaemia; grade 2, mild; grade 3, moderate; grade 4, severe. The grading was based on the assessment of the extent of ischaemia and the completeness of non-enhancement (**Figure 5**). Furthermore, the extent of ischaemia in myometrial tissue was classified into three categories: 1, in the junctional zone; 2, exceeding the junctional zone; 3, up to the serosal surface.

To create uniform criteria for ischaemia evaluation, two radiologists first analysed 30 postprocedural MRIs together. Then both readers interpreted all postprocedural studies independently, and the other repeated the procedure after 1 month. Both radiologists were blinded to the postprocedural pain reports.

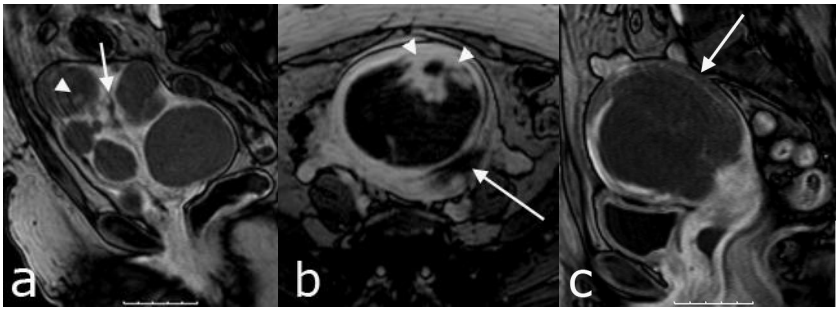


***Figure 5***

*Grading of myometrial ischaemia by MRI. Postprocedural contrast enhanced T1-weighted gradient-echo MR images illustrate the severity of myometrial ischaemia. A sagittal (a) image with multiple leiomyomas shows mild uterine ischaemia (arrow) extending to the endometrium and to the junctional zone. The percentage of leiomyoma ischaemia was estimated to be 98%, because of a small enhancing area in one fibroid (arrowhead). A transverse (b) image shows moderate myometrial ischaemia (arrow) with incomplete dominant leiomyoma ischaemia (arrowheads). A sagittal (c) image shows severe myometrial ischaemia (arrow) extending to the outer serosa with complete leiomyoma ischaemia.*

*Quantitative Preinterventional MRI Measures (Study IV)*

To calculate the dominant leiomyoma-to-skeletal muscle SI-ratio in T2-weighted gradient echo images, two regions of interest (ROIs) were identified; on the cross-sectional area of the dominant leiomyoma and on the iliac muscle (**Figure 6**). The leiomyoma-to-skeletal muscle SI-ratio was calculated.

To calculate contrast-enhancement of the dominant leiomyoma, a ROI identical to that shown in **Figure 6** was drawn on the transverse T1-weighted image before and after the contrast agent injection. The percentage of contrast enhancement was calculated.

To calculate T1 time of the dominant leiomyoma SI was measured from the dominant leiomyoma in each IR image and plotted versus the inversion time. Leiomyoma T1-time was calculated using the data fitting procedure described by Fritz-Hansen et al (Fritz-Hansen *et al.* 1998).

To determine intraobserver variation, the same radiologist repeated the ROI drawing for a sample of 20 patients 6 months later. To determine interobserver variation, another radiologist performed image analysis and the ROI drawing of the same 20 patients.

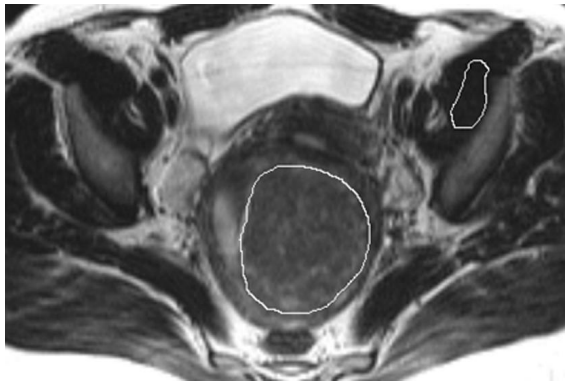

***Figure 6***

*Drawing of regions of interest. The image shows an example of two typical ROIs drawn over the dominant leiomyoma (large ROI) and skeletal muscle for calculating the dominant leiomyoma-to-skeletal muscle SI-ratio.*

## 4.4 TREATMENTS

### 4.4.1 Uterine Artery Embolisation

For premedication oral paracetamol 1g per os and, when needed, diazepam 10 mg for sedation was given. Antibiotic prophylaxis was administered before the procedure with one dose of 1.5 g intravenous cefuroxime natrium and 500 mg metronidazole. After UAE, oral cephalexin monohydras with a dose of 500 mg x 3 and metronidazole with a dose of 400 mg x 2 were started for 5 days. The right femoral artery was accessed with a 5-French introducer sheath under local anaesthesia. A dose of 5000 IU heparin was given in the beginning of the intervention. Digital subtraction angiography of the contralateral internal iliac artery and selective study of the anterior arterial branch was performed with a 4-French diagnostic catheter (Glidecath Cobra, Terumo, Tokyo, Japan) to determine the anatomy of the uterine artery (**Figure 7**).

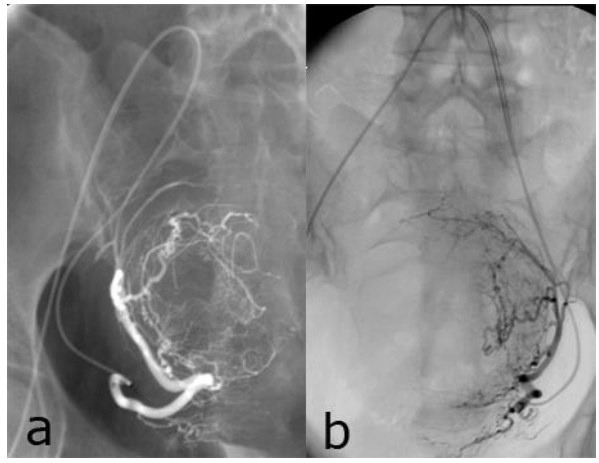


***Figure 7***

*Selective angiography of uterine arteries. Two angiographic images obtained during the initial selective (a) right and (b) left uterine arteriography show the supply of a large leiomyoma.*

Uterine arteriography obtained before embolisation was carefully evaluated with special attention given to the presence of utero-ovarian anastomoses. The catheter was subsequently

advanced into the horizontal portion of the uterine artery. The ipsilateral internal iliac and uterine arteries were then accessed with the same catheter. In tortuous, small, or spastic uterine arteries, catheterisation was performed with a 2.1-French microcatheter to ensure free-flow embolisation. Embolisation was performed by calibrated microsphere particles (550–700 μm; EmboSphere; BioSphere Medical, Louvres, France) in all interventions. The intention was to stop the embolisation when the leiomyoma blood supply is occluded and the flow in the peripheral portion of uterine artery is blocked but there was still sluggish flow in the ascending segment of the uterine artery observed (near-stasis) (**Figures 8 and 9**).

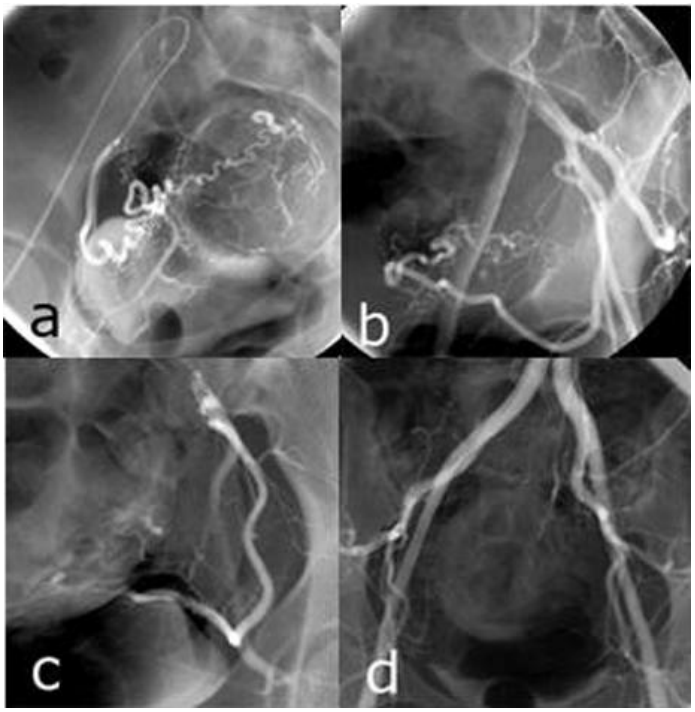


***Figure 8***

*Angiographic images from a patient with one large leiomyoma. (a) Selective right uterine arteriography shows the supply of the large leiomyoma. Images (b) and (c) show the left uterine artery before and after the embolisation. The last image (d) illustrates no supply to the large leiomyoma in the aortography after UAE.*

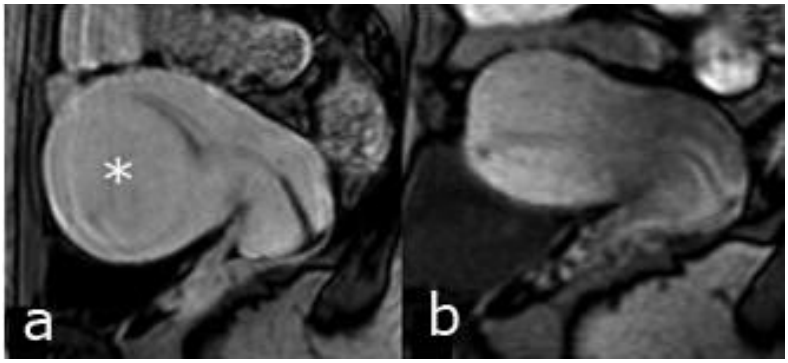


***Figure 9***

*Excellent response to UAE on MRI. (a) Preprocedural contrast enhanced T1-weighted gradient-echo MR image of the same patient than in Figure 8 illustrates the large leiomyoma (asterisk) with intense enhancement (b) The large leiomyoma is not visible on a 3-year follow-up MR image indicating an excellent response to UAE.*

Further, abdominal aortography was performed if there was suspicion of significant additional leiomyoma vasculature from the ovarian artery (**Figures 10 and 11**).

Closure device was routinely used. The same experienced interventional radiologist performed all interventions. During the prolonged intervention intravenous fentanyl 25-50mg for analgesia was given, if needed. In addition, nearly without exception after the intervention prophylactic fentanyl was given before transferring to a recovery room for 4–6 h, after which the patients were transferred to the gynecology ward for further care.

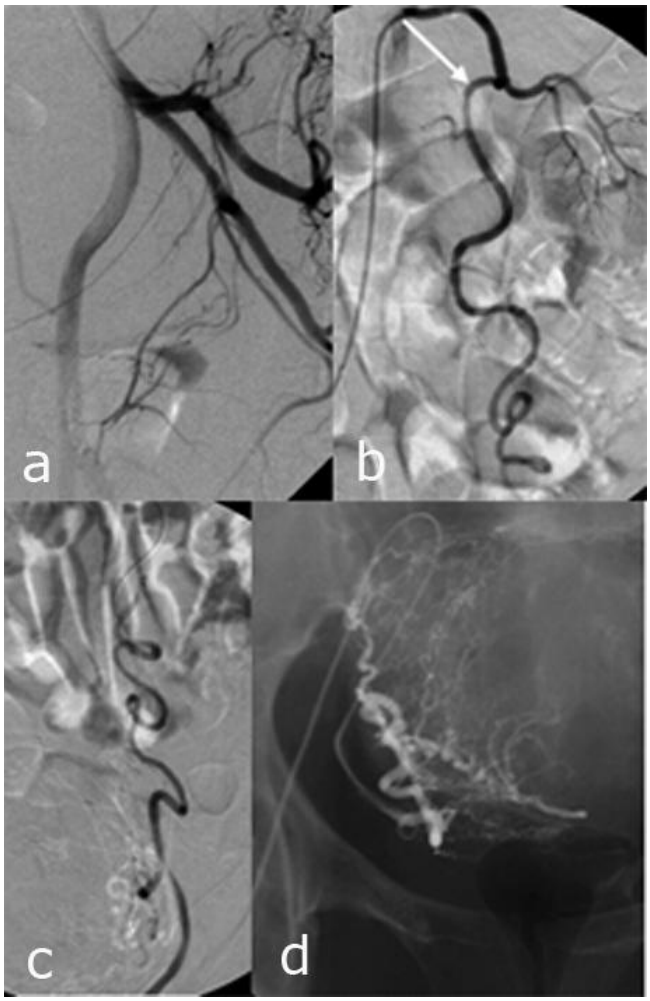


***Figure 10***

*Anatomical variant. (a) Angiography demonstrates a missing left uterine artery. (b) The left ovarian artery (arrow) originates from the left renal artery and supplies the uterus. (c) Angiography after the embolisation shows patent left ovarian artery. (d) Selective angiography demonstrates normal anatomy of the right uterine artery.*

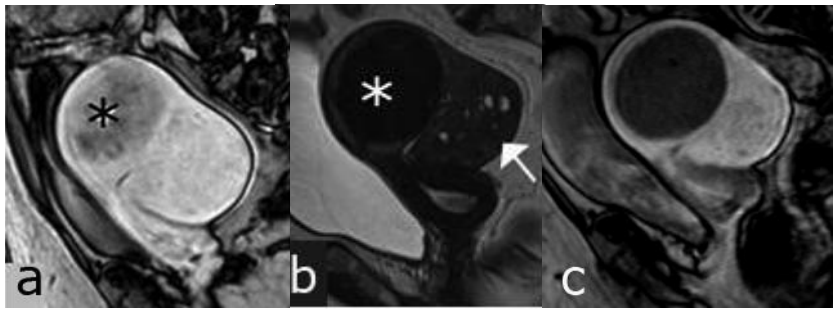


***Figure 11***

*MRI images before and after UAE. (a) Preprocedural contrast enhanced T1-weighted gradient-echo MR image obtained from the same patient than in Figure 10 shows partly degenerated leiomyoma (asterisk) in the anterior part of the uterus. (b) Postprocedural non-enhanced T2-weighted turbo spin echo and (c) enhanced T1-weighted gradient-echo MR images after 3-year follow-up illustrate that the leiomyoma (asterisk) shows no enhancement while adenomyosis (arrow) in the posterior part of the uterus has maintained viable.*

### 4.4.2 Postprocedural Pain and Pain Medication after UAE (Study III)

Postprocedural pain intensity was assessed using the verbal rating scale (VRS) (Williamson *et al.* 2005). The scale ranged from 0 (no pain) to 10 (worst pain imaginable). In-hospital subjective maximal pain levels were assessed at four different times: (1) before leaving the angiography laboratory, (2) in the recovery room, (3) in the gynecology ward and (4) 24 h after UAE. For further analyses, the highest value from among these VRS recordings was registered as the maximal in-hospital pain, and the pain score was classified based on three categories: 1–3, mild; 4–6, moderate; 7–10, severe.

Pain control during the immediate postprocedural recovery period in the recovery room and on the ward was accomplished with ibuprofen and oxycodone. For non-controllable pain, the patient controlled analgesia pump was used. Ibuprofen 800 mg x 3 for one week was started immediately after the procedure. When ibuprofen was contraindicated, paracetamol was given instead.

### 4.4.3 Hysterectomy

The type of hysterectomy (abdominal, vaginal, or laparoscopic-assisted) were not standardised and left to the discretion of the attending gynecologist, in order to maintain the protocol as close to that of daily practice as possible. General anaesthesia was used in all operations.

### 4.4.4 Technical Success and Complications

The technical success of UAE and complications of treatment were defined according to the SIR and CIRSE guidelines (Goodwin *et al.* 2003, Hovsepian *et al.* 2009, Stokes *et al.* 2010). The technical success was defined as occlusion or marked reduction in blood flow in both uterine arteries. Hysterectomies were defined as technically successful if they were performed as planned.

Complications were stratified on the basis of outcome. Major complications resulted in admission to hospital for therapy, an unplanned increase in the level of care, prolonged hospitalisation, permanent adverse sequelae or death; minor complications resulted in no additional interventions and required no therapy or at most nominal therapy or overnight hospital stay for observation only.

### 4.4.5 Recovery

All UAE patients routinely stayed in hospital overnight. They were discharged when there was no longer a need for opiate medication. Periods of sick leave were changed after the first experiences from 3 to 7–10 days.

After hysterectomy the patients were discharged when they could urinate and neither infectious process nor intestinal paralysis occured. Sick leave varied between 3 and 5 weeks. Patients of both groups were encouraged to return to normal life as soon as possible, and they were advised equally to contact the gynecology emergency clinic if any problems appeared.

### 4.4.6 Two-year Follow-up

The same questionnaire concerning symptom characteristics completed at baseline was administered at each follow-up visit. In addition, overall relief of symptoms, changes in menstrual flow, and changes in pressure symptoms compared with baseline were recorded using the following scale: symptom-free, improved, unchanged, or worse; with symptom-free or improved indicating improvement. The measures also included the global health status with the Medical Outcome Study Short Form 36 (SF-36) (Ware *et al.* 1992) at each follow-up visit.

Clinical success was defined according to SIR and CIRSE guidelines as the resolution of presenting symptoms , such as menorrhagia or bulk-related pain, bloating, urinary frequency, or constipation, without additional therapy (Goodwin *et al.* 2003, Hovsepian *et al.* 2009, Stokes *et al.* 2010). Any additional interventions required were recorded.

Satisfaction with treatment was evaluated by asking the patients whether they would choose the performed treatment again at each follow-up visit.

## 4.5 STATISTICAL ANALYSES

In general, continuous variables were tested for normal distribution with the Kolmagorov-Smirnov 1-sample test. The Student's t-test was used to compare normally distributed data and Mann–Whitney U test was used to compare nonparametric, continuous-scale data for non-normally distributed variables (Studies I, II and III). The Pearson Chi-Squared test and Fisher's exact analysis were used for categorical data and dichotomized variables (Studies I, II, and III).

Student's t-test, Mann-Whitney U-test, Pearson's chi-squared test, and Fisher's exact test were used to analyze differences in MRI derived leiomyoma and uterine characteristics with respect to three symptom groups (Study I). In further analyses, the same tests were used to find differences in MRI findings with respect to the presence or absence of

specific pressure and pain symptoms; i.e. increased urinary frequency, urinary stress incontinence, a feeling of pressure on the bowel or back, and non-menstrual related lower abdominal pain (Study I).

In univariate analyses, MRI variables reaching probability (*P*) values less than 0.05 were included in the stepwise multiple logistic regression analyses (Study I). The correlation between the percentage of enhancement of leiomyomas and the size measures of uteri and leiomyomas were assessed with the Spearman's rank correlation coefficient (Study I).

Randomised comparisons of UAE and hysterectomy were performed according to intention to treat (i.e. the analysis considers all randomly assigned patients in their primary assigned groups), and per protocol (i.e. the analysis considers only patients who completed the entire trial receiving the intended treatment) (Study II). For patients who had withdrawn or undergone secondary treatment before the follow-up analysis was performed by taking the last valid observation carried forward (Study II).

Correlation between continuous-scale variables were assessed with the Spearman rank correlation coefficient, and the Kruskal–Wallis test was used to compare continuous-scale variables with respect to categorical variables (Study IV). Correlations that were significant in univariate analyses were further examined in multiple linear regression analyses. In multivariate analyses the multicollinearity of variables was excluded by using collinearity diagnostics (Study IV).

Intra- and interobserver repeatability of the assessments were estimated by calculating kappa coefficients with 95% confidence intervals (CI), and by calculating the intraclass correlation coefficients, the coefficient of variation (Studies III and IV).

A two-tailed *P* value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (SPSS for Windows, Chicago, IL, USA, versions 11.5.1 - 17.0).

# 5 Results

## 5.1 CLINICAL CHARACTERISTICS OF THE PATIENTS

The clinical characteristics of the 122 study patients (Study I) are presented in **Table 5**. A total of 69 (57%) of the 122 women (mean age, 47.5 years; range, 38–60) presented with both menorrhagia and pressure symptoms, while around one-fifth suffered either from menorrhagia alone (n=26 [21%]) or pressure symptoms alone (n=27 [22%]).

Thirteen patients were postmenopausal; 12 of them were receiving hormone replacement therapy, five had menorrhagia, and 12 had pressure symptoms. Thirty patients (32%) with menorrhagia had levonorgestrel releasing intrauterine system (LNG-IUS) without releasing the bleeding symptom. Patients with menorrhagia alone had significantly smaller uteri (measured by bimanual palpation of 'gestational week' size) compared to the other groups (mean 11.2 ± standard deviation (SD) 3.6 [range, 6-22] versus 13.2 ± 2.2 [10-18] and 13.2 ± 3.5 [9-24]).

In Study II the randomly assigned groups were comparable in terms of baseline demographic data, clinical characteristics, symptom severity, and preinterventional MRI findings. None of the randomised patients had MRI features leading to exclusion from the study.

*Table 5*

*Patient characteristics and symptoms at baseline (Study I)*

| Clinical characteristic | Patients (n=122) |
|---|---|
| Age, yrs | 47.5 ± 4.3 (38-60) |
| Postmenopausal [a] | 13 (11) |
| Body mass index | 26.5 ± 4.7 (18-44) |
| Uterus size [b] | 12.8 ± 3.4 (6-24) |
| Levonorgestrel-releasing intrauterine system [a] | 37 (30) |
| Menorrhagia [a] | 95 (78) |
| Duration of menstrual flow, days | 6.1 ± 2.9 (0-16) |
| Hemoglobin level, g/L | 128 ± 17.1 (67-152) |
| Anaemia [a] | 41 (34) |
| Acyclic bleeding [a] | 31 (25) |
| Pressure symptoms [a] | 96 (79) |
| Increased urinary frequency [a] | 68 (56) |
| Urinary stress incontinence [a] | 23 (19) |
| Pain [a] | |
| Dysmenorrhea | 46 (38) |
| Lower abdominal pain | 50 (41) |

Values are mean ± SD (range) unless otherwise specified.
[a] Values are n (%).
[b] Assessed by bimanual palpation as 'gestational week' size.

## 5.2 ASSOCIATION BETWEEN PREINTERVENTIONAL MRI CHARACTERISTICS AND SYMPTOMS (STUDY I)

### 5.2.1 Differences in MRI Characteristics According to Symptom Group (Table 6)

***Patients with Menorrhagia alone versus those with Pressure Symptoms alone***

Leiomyoma with ≥50% protrusion into the uterine cavity was detected in up to 39% of the MRI scans performed on patients with menorrhagia alone, but only in 4% of patients with pressure symptoms alone. Further, the mean percentage of enhanced tissue of leiomyomas was greater in patients with menorrhagia than in those with pressure symptoms. The mean leiomyoma volume and mean uterine width was significantly

smaller in patients with menorrhagia than in those with pressure symptoms.

***Patients with Menorrhagia alone versus those with both Menorrhagia and Pressure Symptoms***

The mean leiomyoma volume was two times larger and the mean anteroposterior diameter and uterine width were significantly greater in patients suffering from both menorrhagia and pressure symptoms compared to those suffering from menorrhagia alone. The mean percentage of enhanced tissue of leiomyomas was significantly greater in patients with menorrhagia alone than in those with both symptoms. The volume of leiomyomas was an independent determinant for distinguishing the two groups in the multiple logistic regression analysis ($P$=0.009).

***Patients with Pressure Symptoms alone versus those with both Menorrhagia and Pressure Symptoms***

The only significant difference in MRI characteristics between patients with pressure symptoms alone and those with both symptoms was that leiomyomas with ≥50% protrusion into the cavity were detected significantly more often in patients with both symptoms.

Three of the patients with only menorrhagia and four of the patients with both symptoms had no submucosal component in any of their leiomyomas; one of them had adenomyosis on MRI, one had a large hemorrhagic leiomyoma, and all of them had 75-100% enhancement in leiomyomas. MRI identified one suspected malignancy, but laparotomy revealed it to be a benign leiomyoma. Adenomyosis was not diagnosed in any patient by transvaginal US but it was detected on MRI in 9 patients, with no differences in the frequency between the three symptom groups. Only two of 122 patients had hemorrhagic degeneration on MRI. Both of them reported non-menstrual related lower abdominal pain and menorrhagia. The percentage of enhancement of leiomyomas correlated inversely with the size measures of uteri and leiomyomas ($-0.307 \geq r \geq -0.477$; $P<0.001$).

*Table 6* *Pairwise comparison of the three patient groups by magnetic resonance imaging characteristic*

| Magnetic resonance imaging characteristic | Menorrhagia alone (n=26) | Pressure symptoms alone (n=27) | *P* value | Menorrhagia alone (n=26) | Menorrhagia and pressure symptoms (n=69) | *P* value | Pressure symptoms alone (n=27) | Menorrhagia and pressure symptoms (n=69) | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| Number of leiomyomas | 5.4 ± 4.6 (1-16) | 6.6 ± 4.6 (1-15) | 0.241 | 5.4 ± 4.6 (1-16) | 6.8 ± 6.1 (1-35) | 0.332 | 6.6 ± 4.6 (1-15) | 6.8 ± 6.1 (1-35) | 0.655 |
| Mean volume of leiomyomas (ml) | 128 ± 129 (7-488) | 203 ± 132 (62-654) | **0.002** | 128 ± 129 (7-488) | 247 ± 308 (12-2279) | **0.006** | 203 ± 132 (62-654) | 247 ± 308 (12-2279) | 0.804 |
| Mean percentage of enhanced tissue of leiomyomas | 90.6 ± 19.5 (10-100) | 85.7 ± 13.7 (50-99) | **0.005** | 90.6 ± 19.5 (10-100) | 86.8 ± 13.4 (40-100) | **0.009** | 85.7 ± 13.7 (50-99) | 86.8 ± 13.4 (40-100) | 0.527 |
| Relationship of leiomyoma to the endometrium [a] | | | | | | | | | |
| ≥50% protrusion into cavity | 10 (39) | 1 (4) | **0.002** | 10 (39) | 18 (26) | 0.648 | 1 (4) | 18 (26) | **0.013** |
| <50% protrusion into cavity | 13 (50) | 21 (78) | 0.969 | 13 (50) | 47 (68) | 0.345 | 21 (78) | 47 (68) | 0.141 |
| Contact with junctional zone | 2 (7) | 3 (11) | | 2 (7) | 2 (3) | | 3 (11) | 2 (3) | |
| No contact with junctional zone | 1 (4) | 2 (7) | | 1 (4) | 2 (3) | | 2 (7) | 2 (3) | |
| Mean uterine length (mm) | 115 ± 25 (82-186) | 112 ± 20 (81-165) | 0.880 | 115 ± 25 (82-186) | 118 ± 30 (73-215) | 0.643 | 112 ± 20 (81-165) | 118 ± 30 (73-215) | 0.476 |
| Mean uterine anteroposterior dimension (mm) | 80 ± 15 (54-120) | 86 ± 15 (54-123) | 0.128 | 80 ± 15 (54-120) | 92 ± 26 (57-215) | **0.020** | 86 ± 15 (54-123) | 92 ± 26 (57-215) | 0.593 |
| Mean uterine width (mm) | 87 ± 21 (61-152) | 98 ± 16 (73-137) | **0.006** | 87 ± 21 (61-152) | 95 ± 24 (60-197) | **0.036** | 98 ± 16 (73-137) | 95 ± 24 (60-197) | 0.383 |
| Mean uterine volume (ml) | 396 ± 262 (119-1362) | 424 ± 163 (254-796) | 0.122 | 396 ± 262 (119-1362) | 526 ± 378 (149-2383) | 0.062 | 424 ± 163 (254-796) | 526 ± 378 (149-2383) | 0.596 |
| Hemorrhagic degeneration [a] | 2 (8) | 0 | 0.236 | 2 (8) | 0 | 0.073 | 0 | 0 | |
| Adenomyosis [a] | 2 (8) | 3 (11) | 1.000 | 2 (8) | 4 (6) | 0.664 | 3 (11) | 4 (6) | 0.397 |

Values are mean ± SD (range) unless otherwise specified. [a] Values are n (%).

### 5.2.2. MRI Characteristics in Patients with Specific Pressure and Pain Symptoms

In further analyses, differences in MRI findings were evaluated and the patients were categorized with respect to the presence or absence of each individual pressure and pain symptoms. **Table 7** demonstrates the significant MRI characteristics that distinguish symptomatic patients from non-symptomatic patients with respect to increased urinary frequency, stress incontinence, lower abdominal pain, and a feeling of pressure on the bowel and back. The table shows that MRI measures of uterine and leiomyoma size, and the low degree of enhancement in leiomyoma tissue, were all significantly associated with increased urinary frequency. The length of the uterus proved to be an independent determinant for increased urinary frequency in multiple logistic regression analysis ($P$=0.021).

The number of leiomyomas, the relationship of leiomyomas to the endometrium, and the presence of hemorrhagic degeneration or adenomyosis were not associated with any specific pressure or pain symptoms. Further, none of the MRI characteristics were associated with urinary stress incontinence, with non-menstrual related-pain in the lower abdomen, or with a feeling of pressure on the back.

*Table 7*

*Association between magnetic resonance imaging characteristics and specific pressure and pain symptoms*

| | Symptom | | | | |
|---|---|---|---|---|---|
| **Magnetic resonance imaging characteristic** [a] | **Increased urinary frequency (n=68 vs n=54)** | **Stress incontinence (n=23 vs n=99)** | **Lower abdominal pain (n=50 vs n=72)** | **Pressure feeling to bowel (n=27 vs n=95)** | **Pressure feeling to back (n=25 vs n=97)** |
| Mean volume of leiomyomas (ml) | 239 vs 178, ***P*=0.002** | 199 vs 215, *P*=0.716 | 198 vs 222, *P*=0.803 | 291 vs 190, *P*=0.589 | 223 vs 209, *P*=0.592 |
| Mean uterus length (mm) | 122 vs 110, ***P*=0.032** | 117 vs 116, *P*=0.919 | 114 vs 118, *P*=0.510 | 112 vs 118, *P*=0.419 | 112 vs 117, *P*=0.236 |
| Mean uterus ap-diameter (mm) | 92 vs 83, ***P*=0.005** | 89 vs 88, *P*=0.961 | 86 vs 89, *P*=0.527 | 95 vs 86, *P*=0.217 | 92 vs 87, *P*=0.318 |
| Mean uterus width (mm) | 97 vs 90, ***P*=0.011** | 93 vs 94, *P*=0.806 | 91 vs 96, *P*=0.310 | 99 vs 93, *P*=0.531 | 94 vs 94, *P*=0.809 |
| Mean uterus volume (ml) | 524 vs 415, ***P*=0.003** | 470 vs 477, *P*=0.651 | 446 vs 497, *P*=0.635 | 551 vs 455, *P*=0.825 | 496 vs 471, *P*=0.731 |
| Mean percentage of enhanced tissue of leiomyomas | 86.8 vs 88.1, ***P*=0.022** | 92.0 vs 86.3, *P*=0.242 | 86.6 vs 87.9, *P*=0.592 | 84.5 vs 88.2, ***P*=0.049** | 87.2 vs 87.4, *P*=0.451 |

[a] Only significant magnetic resonance imaging characteristics that distinguish symptomatic patients from non-symptomatic patients with respect to specific pressure and pain symptoms.

## 5.3 COMPARISON OF UAE AND HYSTERECTOMY BY INTENTION-TO-TREAT (STUDY II)

### 5.3.1 Technical Success and Complications

Technical success of the treatments performed was 25/27 (93%) in the UAE group and 21/26 (81%) in the hysterectomy group (*P*=0.204). Two (7%) of the UAE patients received unilateral UAE because of a hypoplastic left uterine artery. One crossover patient from the UAE group underwent vaginal hysterectomy successfully. Procedures in the hysterectomy group included 16 (61%) abdominal hysterectomies, 7 (27%) vaginal hysterectomies and 3 (12%) laparoscopic-assisted vaginal hysterectomies. In the hysterectomy group, 5/26 (19%) vaginal or laparoscopic hysterectomies were converted to abdominal hysterectomy owing to technical difficulties.

None of the UAE patients but two hysterectomy patients (7%) encountered major complications (*P*=0.492); one relaparotomy because of urinary bladder lesion, and one patient encountered postoperative haematoma and infection. One UAE patient encountered a groin haematoma that required no specific treatment.

### 5.3.2 Recovery

Recovery was faster in the UAE group than in the hysterectomy group. Mean length of sick leave was significantly shorter after UAE than after hysterectomy (10.8 days versus 34.9 days; *P*=0.001). Patients discharged from hospital significantly earlier after UAE than after hysterectomy (mean 1.3 days versus 3.5 days; *P*=0.001).

### 5.3.3 Two-year Follow-up Results

#### 5.3.3.1 Improvement of Symptoms

The improvement of symptoms during the 2-year period is presented in **Figure 12**. Overall relief of symptoms was good in both groups; 22 (82%) of the UAE patients and 28 (93%) of the hysterectomy patients reported total or substantial relief of

symptoms. Among patients with menorrhagia, 12/18 (67%) had total or substantial improvement after UAE. Among patients with pressure symptoms, total or substantial improvement was reported significantly more often by patients in the UAE group than by patients in the hysterectomy group (19/20 [95%] versus 18/26 [69%]. There was more urinary bladder symptoms after hysterectomy than after UAE (9 [30%] versus 2 [7%]; *P*=0.031). Occurrence of urinary stress incontinence was even increased among hysterectomy patients being 13 [43%] versus 7 among [26%] UAE patients (*P*=0.169).

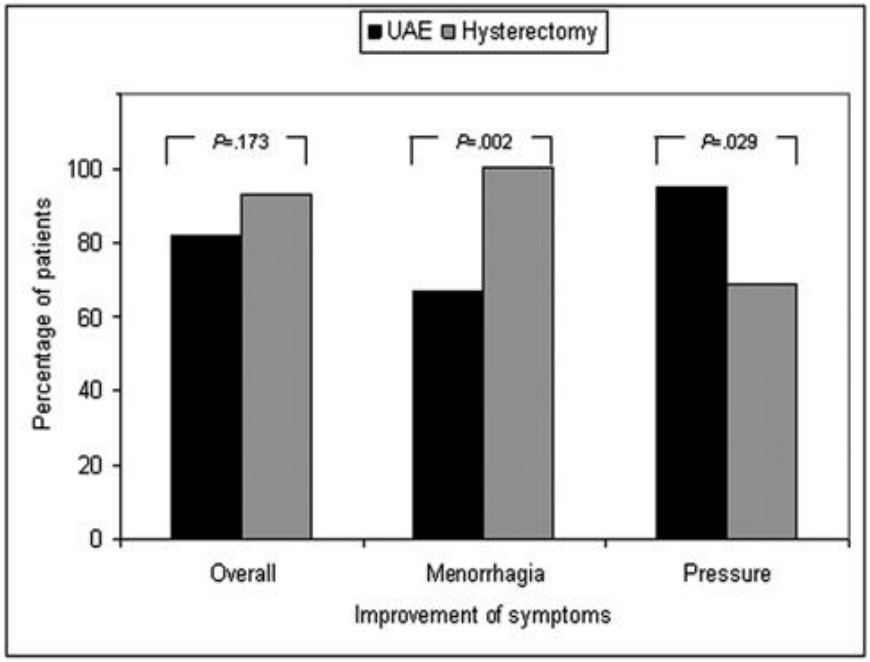


***Figure 12***

*Total or substantial improvement of symptoms after UAE and hysterectomy at 2-year follow-up. Data analyzed by intention-to-treat show that significantly better improvement of menorrhagia was reported by hysterectomy patients while significantly better improvement of pressure symptoms was reported by UAE patients, but there was no difference in overall improvement of symptoms.*

#### 5.3.3.2 Clinical Success and Additional Treatments

A clinical success rate of 81% was registered in the UAE group compared with 90% in the hysterectomy group (*P*=0.238). Five of the 27 patients (19%) in the UAE group required an additional invasive procedure during the follow-up: three hysteroscopies and 3 hysterectomies for continued bleeding or pain. Thus, the rate of secondary hysterectomies at 2 years was 12%.

Three of the 30 patients (10%) in the hysterectomy group required additional treatment because of continuing symptoms; laparotomy for pain, and hysteroscopic myomectomy or insertion of LNG-IUS was performed for two of four primarily untreated patients because of bleeding symptoms.

#### 5.3.3.3 Satisfaction to the Treatment

The majority of patients would have chosen their performed treatment again in both groups after two years: 24 [89%] patients in the UAE group versus 29 [97%] patients in the hysterectomy group (*P*=0.336).

The aforementioned results were calculated by using per protocol analysis as well. There was a trend towards better results in the UAE group concerning pressure relief on the urinary bladder and improvement of pressure symptoms at 2 years but these differences were not statistically significant (p=0.123 and p=0.477, respectively). Otherwise, per protocol analysis demonstrated no substantial differences compared with the results reported above.

## 5.4 POSTPROCEDURAL PAIN AFTER UAE AND MYOMETRIAL AND LEIOMYOMA ISCHAEMIA ON 24 H MRI (STUDY III)

The mean volume of embolisation agent used was 6 ml (median, 6 ml; range, 2–18 ml). In 27 patients (44%) the endpoint of embolisation was stasis of both uterine arteries; in the remainder of patients, either one (29 patients) or both uterine

arteries (5 patients) were embolised only to near-stasis. For one patient the endpoint was not recorded.

### 5.4.1 Postprocedural Pain

The mean maximal in-hospital VRS value was 7.7 (median, 8.0; range, 1–10); the maximal pain was severe in 46 patients, moderate in 11 patients and mild in 5 patients.

The mean maximal pain score was 4.2 in the angiography laboratory right after UAE and 7.5 in the recovery room, i.e. 1–6 h after embolisation, where 54 patients (87%) reported their highest pain score. The pain level diminished gradually, and the mean maximal pain score was on the ward 5.1 and at the time of the follow-up MRI, about 24 h after UAE, 1.9. At that time, 44 patients (71%) reported only mild residual pain.

### 5.4.2 Ischaemia on MRI

In MRI analysis severe or moderate myometrial ischaemia that exceeded the junctional zone was in about one-half of the patients. The mean percentage of ischaemic tissue in the myometrium by two readers was 18%/20% and in leiomyoamas 92%/93%. The mean ischaemic volume assessed in the myometrium was 35ml/38 ml, whereas the mean ischaemic volume in the leiomyomas was 177ml/179 ml.

### 5.4.3 Determinants of Maximal In-hospital Postprocedural Pain

The severity of myometrial ischaemia, the percentage and volume of ischaemic tissue in the myometrium, and the volume of embolisation agent significantly positively correlated with severe maximal in-hospital pain (**Figure 13**). Patients with moderate or severe myometrial ischaemia reported severe pain more frequently than those with only mild myometrial ischaemia (28/33 [85%] versus 18/29 [62%], $P$=0.041). The mean percentage and the mean volume of ischaemic tissue in myometrium were higher in patients who reported severe pain than in those who reported only moderate or mild pain (mean 23% versus mean 11%, and mean 45 ml versus mean 20 ml).

Patients embolised with more than 6 ml embolisation agent reported severe pain more frequently than those embolised with less than 6 ml (24/27 [89%] versus 22/35 [63%], *P*=0.038).

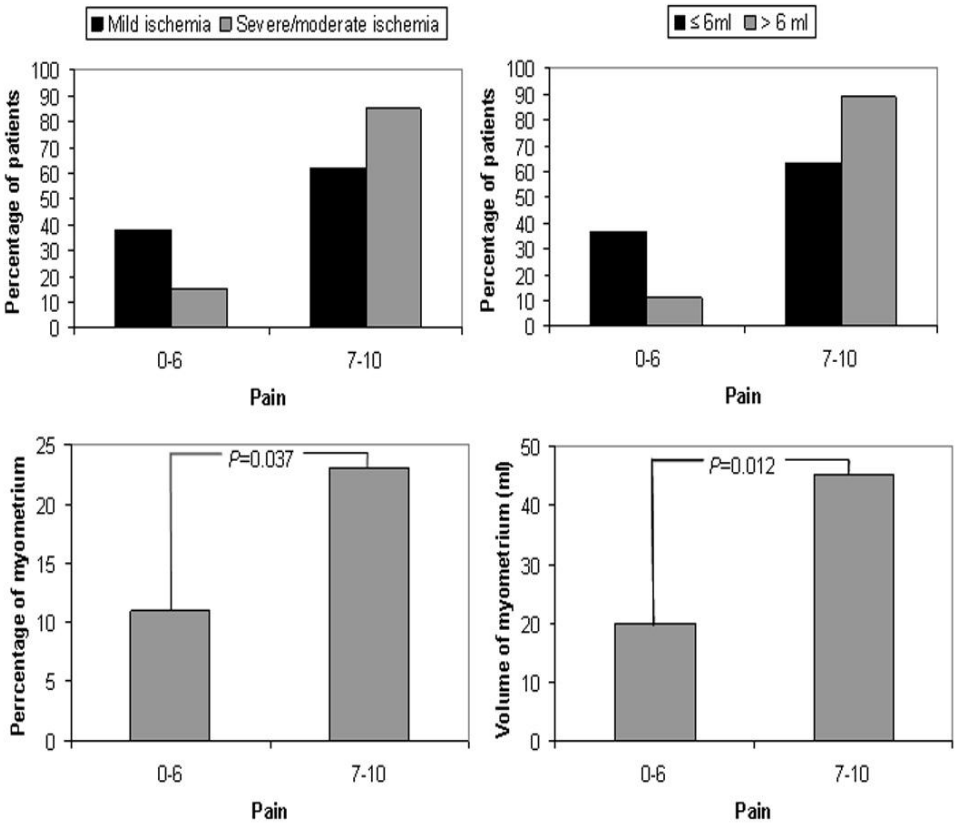


***Figure 13***

*Determinants of maximal in-hospital postprocedural pain after UAE. The bar graph shows that patients with moderate or severe myometrial ischaemia reported severe pain more frequently than those with only mild myometrial ischaemia (a). Patients embolised with more than 6 ml embolisation agent reported severe pain more frequently than those embolised with less than 6 ml (b). The mean percentage (c) and the mean volume (d) of ischaemic tissue in myometrium were higher in patients who reported severe pain than in those who reported only moderate or mild pain.*

The factors that showed no association with maximal in-hospital pain were preinterventional volume of the uterine corpus and of the leiomyomas, the end-point of embolisation achieved, and leiomyoma ischaemia on the 24-h MRI.

### 5.4.4 Determinants of Ischaemia on MRI

When the endpoint was stasis in both uterine arteries (27 patients), the mean percentage of ischaemic tissue was significantly higher in leiomyomas compared with patients in whom both or one uterine artery was embolised only to near-stasis (34 patients) (96% versus 89%, *P*=0.017). In addition, uteri embolised with more than 6 ml of embolisation agent (27 patients) had larger volumes of ischaemic leiomyoma tissue than those embolised with 6 ml or less (35 patients) (233 ml versus 132 ml, *P*=0.023). Further, the use of a large volume of embolisation agent (more than 6 ml) was associated with a large leiomyoma volume (mean 259 ml versus 153 ml, *P*=0.031) and with a large uterine corpus volume (519 ml versus 340 ml, *P*=0.020) on preinterventional MRI. On the other hand, uteri embolised with 6 ml or less of embolisation agent showed severe or moderate myometrial ischaemia more frequently than those embolised with more than 6 ml (23/35 [66%] versus 10/27 [37%], *P*=0.025). Further, patients with moderate or severe myometrial ischaemia had a smaller uterine corpus (347 ml versus 498 ml, *P*=0.008) than those with only mild ischaemia.

### 5.4.5 Repeatability of MRI Measurements

Intraobserver repeatability and interobserver reproducibility of the evaluations of severity of myometrial ischaemia were high (intra- and interrater κ were 0.87 and 0.74, respectively). The intra-and interrater κ for assessing the extent of myometrial ischaemia was 0.76 and 0.31 indicating lower interrater repeatability. The intra- and interobserver repeatability were moderate for percentage of ischaemic myometrial tissue (CV% 24% and 24%, respectively) and high for ischaemic leiomyoma tissue (CV% 2% and 3%, respectively).

## 5.5 PREDICTIVE VALUE OF MRI MEASURES IN UTERUS AND DOMINANT LEIOMYOMA SIZE REDUCTIONS (STUDY IV)

### 5.5.1 Uterus and Dominant Leiomyoma Size Reductions after UAE

During the 6-month follow-up after the UAE, both the uterus and dominant leiomyoma sizes decreased in 49 patients (94%). The mean uterus size reduction was 156 mL ± 131 (range, -51-592 mL), where the minus sign indicates an enlargement, and the mean dominant leiomyoma size reduction was 55 mL ± 66 (range, -82-257 mL). The percentages of uterus and dominant leiomyoma size reductions were 33% ± 21 (range, -23-67%) and 44% ± 31 (range, -43-100%), respectively.

### 5.5.2 Correlation between Preinterventional MRI Measures and Uterus and Dominant Leiomyoma Size Reduction

T1 time and leiomyoma-to-skeletal muscle T2 SI-ratio were significantly positively correlated with both uterus (0.440 and 0.470, respectively) and leiomyoma (0.338 and 0.258, respectively) size reductions assessed by Spearman's rank correlation analysis. The contrast enhancement, size, or location of dominant leiomyoma was not associated with size reductions.

### 5.5.3 Diagnostic Performance Predictions of Uterus and Leiomyoma Size Reductions

Leiomyoma-to-skeletal muscle T2 SI-ratio, T1 time, and contrast enhancement were useful MRI measures for predicting uterus and leiomyoma size reductions. The highest accuracy for the predictions was given by leiomyoma- to-skeletal muscle T2 SI-ratio to predict ≥75% leiomyoma size reductions (Az = 0.930; 95% CI: 0.853, 1.000). **Table 8** summarizes the points on the receiver operating characteristic (ROC) curve for each MRI measure that were closest to the coordinates (0,1) for diagnosing size reduction and the corresponding values of diagnostic performance.

***Table 8***

*Diagnostic performance of magnetic resonance imaging features in discriminating patients with and without ≥50% and ≥75% leiomyoma and ≥50% uterus size reductions*

| Magnetic resonance imaging feature | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|
| ≥ 50% leiomyoma size reduction | | | | | |
| T1-time ≥ 700 msec | 73 | 64 | 64 | 73 | 68 |
| Leiomyoma-to-skeletal muscle T2 SI ratio ≥1.9 | 77 | 60 | 63 | 75 | 68 |
| ≥ 75% leiomyoma size reduction | | | | | |
| T1-time ≥ 750 msec | 86 | 67 | 32 | 96 | 70 |
| Leiomyoma-to-skeletal muscle T2 SI ratio ≥ 3.5 | 100 | 92 | 70 | 100 | 93 |
| ≥ 50% uterus size reduction | | | | | |
| Leiomyoma-to-skeletal muscle T2 SI ratio ≥ 2.5 | 77 | 82 | 63 | 90 | 81 |
| Contrast-enhancement ≥ 105% | 85 | 62 | 46 | 91 | 68 |

High leiomyoma-to-skeletal muscle T2 SI-ratio and T1 time had high sensitivities and specificities in identifying patients with ≥50% or ≥75% leiomyoma size reductions. Further, high leiomyoma-to-skeletal muscle T2 SI-ratio (**Fig 14**) had high sensitivities and specificities in identifying patients that had ≥50% uterus size reductions.

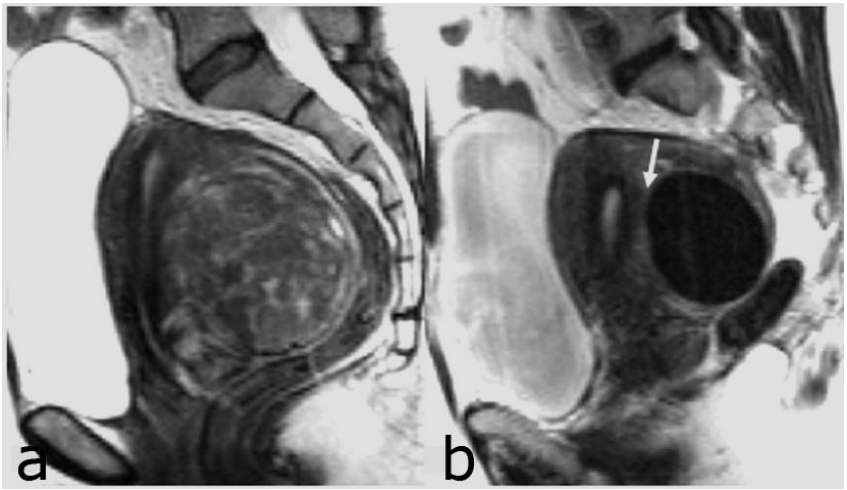


***Figure 14***

*Leiomyoma size reduction on MRI at 6-month follow-up. Sagittal preprocedural T2-weighted image (a) demonstrates a relatively high SI of the leiomyoma (leiomyoma-to-muscle T2 SI-ratio = 3.4). Six-month follow-up image (b) shows that the leiomyoma had diminished by 63%. Note there is no contact in the endometrium anymore (arrow).*

### 5.5.4 Repeatability of MRI Measurements

In Study IV the T1 time measure had the least variation in intra- and interobserver measurements (CV% 4% and 11%, respectively). Intra- and interobserver repeatability for leiomyoma-to-skeletal muscle T2 SI ratio (CV% 15% and 27%, respectively) and for contrast enhancement (CV% 17% and 15%, respectively) were lower.

# 6 Discussion

In the present study, two treatments, UAE and hysterectomy, for symptomatic patients with uterine leiomyomas were prospectively compared at mid-term follow-up. New aspects of the use of MRI to evaluate the association of various symptoms and imaging findings of uterine leiomyomas, to assess the leiomyoma and myometrial ischaemia after UAE in considering the postprocedural pain, and to predict the uterine and leiomyoma size reduction after UAE, were sought.

## 6.1 ASSOCIATIONS BETWEEN PATIENT SYMPTOMS AND MRI FINDINGS (STUDY I)

The Study I utilizes the excellent anatomical visualization of uterine leiomyomas by MRI to study the association between patient's symptoms and MRI characteristics of leiomyomas.

*Menorrhagia and Relationship of Leiomyomas to Endometrium*

It has been a common clinical suggestion that a submucosal leiomyoma is strongly associated with menorrhagia. Our analysis showed that the degree of submucosal extension has an influence on menorrhagia. Indeed, the proportion of women having submucosal leiomyomas with ≥50% protrusion into the uterine cavity was significantly greater among patients with menorrhagia compared to those without menorrhagia. In addition, a minor submucosal component protruding into the cavity had no implication for the bleeding symptom.

MRI is an ideal tool for evaluating the characteristics of large uterine leiomyomas, especially the leiomyoma location and submucosal leiomyoma extent (Dueholm *et al.* 2001, Spielmann *et al.* 2006). In previous MRI studies the results concerning the relationship between menorrhagia and leiomyoma location have

been controversial. One MRI study with 23 patients showed that leiomyomas associated with hypermenorrhea anatomically disrupted the junctional zone (Hricak *et al.* 1986). Further, Sulaiman et al. found in a retrospective study that menstrual blood loss was associated with a submucosal location on MRI (Sulaiman *et al.* 2004). On the other hand, one study that prospectively followed 46 patients by MRI reported that a submucosal location was not associated with leiomyoma related symptoms (Arleo *et al.* 2007). Previous US studies have also shown mixed results. Similar to our findings, one cross-sectional US study of non-care-seeking women showed that the tissue layer location of leiomyomas was related to menstrual cycle characteristics (Marino *et al.* 2004). Another prospective ultrasound study of 80 patients with abnormal bleeding found that an intramural location was also associated with increased bleeding complaints (Clevenger-Hoeft *et al.* 1999). In contrast, in a study of a random sample of women, the risk for heavy menstrual bleeding was not related to leiomyoma location (Wegienka *et al.* 2003).

However, in the present study seven patients with menorrhagia had no submucosal component in their leiomyomas. There must also be another mechanism that leads to heavy bleeding. In fact, according to a review article of Osei et al. there are women who suffer from heavy bleeding without apparent uterine pathology (Osei *et al.* 2005).

***Enhancement of Leiomyomas***

One of our study aims was to clarify the possible association of enhancement in leiomyomas with symptoms. This issue has not been evaluated before. We used a similar visual analysis of the percentage enhancement of leiomyomas as we did for analysing nonenhancement of leiomyomas after UAE (Study III). The leiomyomas of the patients suffering from menorrhagia showed a significantly higher degree of enhancement than the leiomyomas of the patients with pressure symptoms. In other words, intense enhancement of leiomyomas may contribute to heavy bleeding. On the other hand, although the enhancement

of leiomyomas correlated inversely with leiomyoma size, it was not an independent determinant in the multiple logistic regression analysis.

***Size Measures of Uteri and Leiomyomas***

As expected, the sizes of uteri and leiomyomas among patients with pressure symptoms were significantly greater than among those without, thus leiomyomas were smaller among patients with only menorrhagia.

***Association of MRI Characteristics with Increased Urinary Frequency, Stress Incontinence, Lower Abdominal Pain, and Feeling of Pressure on the Bowel and Back***

Pressure complaints are a heterogenous group of various symptoms and the term 'pressure symptom' is sometimes difficult to interpret; patients suffer from the feeling of uncomfortable pressure in their pelvic region. Most studies have evaluated only a few symptoms and mainly the volume of the largest leiomyoma, instead of the volume of all leiomyomas, has been used. The results showed that increased urinary frequency seems to be associated with large leiomyomas and uteri. Indeed, in the Ontario trial the urinary frequency and urgency were greatly or moderately improved in 68% of 306 women following a mean 35% volume reduction in a leiomyomata uterus after UAE, indicating that leiomyomas are truly associated with urinary symptoms (Pron *et al.* 2003c). In contrast to our results, another prospective MRI study found that the total uterine volume was not associated with leiomyoma-related symptoms (Arleo *et al.* 2007).

A study by Murase et al. implied that hemorrhagic degeneration in particular may be concurrent with pain symptoms (Murase *et al.* 1999). We found hemorrhagic degeneration by MRI in only two of our patients, both of whom reported non-menstrual related lower abdominal pain. Thus, the number of patients with this type of degeneration was too small to warrant any conclusions about the relationship between hemorrhagic degeneration and symptoms.

*Symptoms not Associated with MRI Characteristics*

It has been suggested that a large number of leiomyomas is associated with symptom severity (Buttram *et al.* 1981, Vollenhoven *et al.* 1990). Our findings do not support this as the number of leiomyomas was not associated with any symptom.

While various patient complaints are often attributed to leiomyomas, it is probable that not all pressure and pain symptoms are leiomyoma-related. In our study, urinary stress incontinence, non-menstrual related lower abdomen pain, and a feeling of pressure on the back were not associated with any MRI characteristics. Therefore, further investigation to exclude other etiologies such as in the case of urinary stress incontinence and in the case of abdominal pain, may be prudent. We agree with the conclusions by Hutchins that other predisposing factors should be considered in patients with leiomyomas and chronic pelvic pain (Hutchins 1995). This is also supported by the findings in a population-based ultrasound study of non-care-seeking patients where the occurrence of pelvic pain had no correlation with leiomyoma volume or number (Lippman *et al.* 2003).

Preprocedural MRI could help detect other possible causes of pain or pressure complaints, such as adenomyosis, pelvic varices, endometriosis, pelvic inflammatory disease, or bowel- or spine-associated causes. Actually, in our study population there was no suspicion of adenomyosis by transvaginal US, but adenomyosis was found by MRI in 7% of patients.

*Strength and Limitations of Study I*

Our patient population is larger than those in other studies focusing on the association between MRI findings and symptoms of leiomyomata patients. Further, none of the consecutive patients was excluded due to any specific symptom.

It should be noted that the study group consisted of patients with treatment demanding symptoms. In order to clarify a general view of the association between MRI and clinical characteristics of leiomyoma patients, symptom-free women with leiomyomas should be included as a control group.

Further, the reproducibility of the preinterventional MRI assessment was not analyzed for Study I. However, previous studies have shown that MRI assessment of uterine leiomyomas has good inter- and intraobserver reproducibility (Dueholm *et al.* 2002, Volkers *et al.* 2008b).

## 6.2 COMPARISON OF UAE AND HYSTERECTOMY (STUDY II)

### *Randomisation*

Thus far, only three randomised trials comparing UAE and hysterectomy have been carried out (Table 1): a Spanish singlecenter trial (Pinto *et al.* 2003), a multicenter REST trial in the UK (Edwards *et al.* 2007), and a multicenter EMMY trial in the Netherlands (Volkers *et al.* 2007). EMMY trial recently published the 5-year outcome (van der Kooij *et al.* 2010). In the multicenter trials most individual centers have included only a small number of patients resulting in a large number of participating hospitals with heterogeneous technical performance and previous experience with UAE, complicating the interpretation and judgement of the general clinical applicability of the results.

Our randomised sample size was small. Attempts to randomise more patients in a reasonable time failed because of difficulties in recruitment. During study period, of the patients requiring treatment for leiomyomas, 26% were recruited to the study, and 42% of eligible patients were randomised. Many of our study patients refused to randomise and preferred UAE (n=60) to avoid an invasive operation, and on the other hand, many women preferred hysterectomy (n=18) as a definitive treatment. Many aspects effect on the patients' opinion on severing their uteri including the cultural aspects in different countries. Data from Nevadunsky suggested that many women consider the uterus an important aspect of their feminity and sexual image (Nevadunsky *et al.* 2001). Also, in the EMMY trial only 51% of eligible patients agreed to be randomised and it took 2 years to gather 177 patients from 28 participating

hospitals (Hehenkamp *et al.* 2005). REST investigators also had difficulties in recruitment (Edwards *et al.* 2007). Despite the small number of patients in our study groups, they were well balanced concerning symptoms and MRI findings after randomisation. In addition, one experienced interventional radiologist performed all embolisations, providing a uniform technique.

The strength of our trial is that the research population was unselected; patients were not excluded according to the presenting symptoms. Only one of the earlier randomised trials, REST study (Edwards *et al.* 2007), included both menorrhagia and pressure symptoms in the inclusion criterias and there was no limit on the size or number of leiomyomas, but there were a large number of participating hospitals like in EMMY trial (Volkers *et al.* 2007). In addition, EMMY trial excluded patients with submucosal leiomyomas and patients who had exclusively bulk-related symptoms and/ or pain but no menorrhagia. In the study by Pinto et al. (Pinto *et al.* 2003), the inclusion criterion also was menorrhagia only, and the patients with leiomyomas larger than 10 cm in diameter were excluded.

***Complications and Recovery***

Our finding of a higher major complication rate with hysterectomy (7%) than with UAE was not statistically significant. In most previous studies a major complication rate was higher in patients with hysterectomy (Dutton *et al.* 2007, Edwards *et al.* 2007, Pinto *et al.* 2003, Spies *et al.* 2004b). In contrary, EMMY trial showed no statistically significant differences between the treatment groups (Hehenkamp *et al.* 2005). The explanation for these divergent results could be variable inclusion criteria in the individual studies. Considering the major complications after hysterectomy, laparoscopic and vaginal hysterectomies have become more common during recent years in Finland and the overall incidence of major complications has decreased (Brummer *et al.* 2008).

In the present study patients in the UAE group recovered faster than patients in the hysterectomy group, confirming the

results of earlier studies (Edwards *et al.* 2007, Hehenkamp *et al.* 2006, Pinto *et al.* 2003, Spies *et al.* 2004b). There also is evidence for shorter hospital stay and quicker return to work in other mini-invasive treatment options such as magnetic resonance-guided focused ultrasound, laparoscopic uterine artery occlusion, and cryomyolysis when compared to hysterectomy (Sharp 2006).

***Two-year Follow-up Results***

The results showed that UAE gave good overall relief of symptoms, comparable to hysterectomy. In contrary, the REST trial reported significantly better symptom scores in the surgical group at one year (Edwards *et al.* 2007). Further, more women in the hysterectomy cohort reported relief of leiomyoma symptoms (89% versus 80%) and feeling better (81% versus 74%) in a multicenter retrospective HOPEFUL study (Dutton *et al.* 2007).

Of patients with menorrhagia in the UAE group, improvement was reported by two-thirds in the present study. This result is comparable with those of previous randomised studies (Pinto *et al.* 2003, Volkers *et al.* 2007).

A new finding in the study was that significantly better improvement of pressure symptoms was reported by UAE patients. Thus, our findings imply that UAE is preferable to hysterectomy in patients suffering from pressure symptoms. In particular, there were significantly more pressure symptoms of the bladder and more urinary stress incontinence after hysterectomy than after UAE. Similarly, significantly more of women reported worsening urinary symptoms after hysterectomy (27%) than after UAE (8%) in HOPEFUL study (Hirst *et al.* 2008). Thus, it seems that the term "pressure symptom" is unspecific and includes the possibility that other causes than leiomyomas are the etiology of these symptoms. The results of our Study I also implies that. In addition, hysterectomy seems to increase the risk of urinary incontinence (Altman *et al.* 2007, Brooks *et al.* 2009). On the other hand, in EMMY trial there were no differences in improvement of bulk-related symptoms between groups at 2-years (Volkers *et al.*

2007). However, in EMMY trial better improvement of defecation function was found after UAE at 5-year follow-up comparing to hysterectomy (van der Kooij *et al.* 2010).

Our findings indicated that UAE was not inferior to hysterectomy considering patients' satisfaction after two years. This was in concordance with two other randomised trials (Edwards *et al.* 2007, Pinto *et al.* 2003). Conversely, in the EMMY trial the patients in the hysterectomy group were significantly more satisfied after two years than those in the UAE group (Hehenkamp *et al.* 2008), but at 5-year follow-up there was no difference (van der Kooij *et al.* 2010).

The trend in treatment for leiomyomas is toward a more conservative approach (Jacobson *et al.* 2007). Jacobson et al. evaluated data regarding uterine conserving procedures for the treatment of leiomyomas (Jacobson *et al.* 2007). The study was based on the clinical database of women >20 years with symptomatic leiomyomas from 1997 to 2003 in a Northern California population. They noticed that during these years the increase in rate of UAE had the greatest impact on treatment, possibly replacing hysterectomy. However, they also reported that rate of hysterectomy after initial uterine conserving procedures reached 17.7% for UAE (Jacobson *et al.* 2007), being in concordance with other trials and our study: two years after UAE, 12% of patients had undergone a secondary hysterectomy. This is equal to the finding in the REST (Edwards *et al.* 2007), but a lower rate than that in the EMMY trial (Volkers *et al.* 2007). After 5 years the rate of hysterectomy after UAE was 28% in EMMY trial, all because of uncontrolled menorrhagia (van der Kooij *et al.* 2010). Thus, the patients have to be informed that heavy bleeding may be decreased but not eliminated completely and there may be a need for an additional treatment. The total need for additional interventions for symptom control after UAE in our study was comparable with the results of EMMY and REST trials (Edwards *et al.* 2007, Volkers *et al.* 2007).

### 6.3 POSTPROCEDURAL PAIN AFTER UAE AND UTERINE ISCHAEMIA ON MRI (STUDY III)

In Study III, the extent and severity of uterine ischaemia on MRI one-day post-procedure were used to evaluate the association between the severity of postprocedural pain and myometrial and leiomyoma ischaemia after UAE. Although findings from several MRI follow-up studies have shown that myometrial perfusion recovers (Banovac *et al.* 2002, deSouza *et al.* 2002, Jha *et al.* 2000, Katsumori *et al.* 2001, Pelage *et al.* 2000), even then, transient myometrial ischaemia can be an important clinical issue because it can contribute to postprocedural pain following UAE (Sterling *et al.* 2002).

*Determinants of Postprocedural Pain*

Our results show the importance of myometrial ischaemia in the pathophysiology of frequent, often severe postprocedural pain. Indeed, severe maximal inhospital pain correlated positively with myometrial ischaemia, but not with leiomyoma ischaemia. Although uterine ischaemia was detected in all patients by MRI, only about 20% of the myometrial tissue was ischaemic, while about 90% of leiomyoma tissue was ischaemic. These data indicate that leiomyoma tissue is more vulnerable to embolisation than the myometrium. Scheurig-Muenkler et al. also showed that complete reperfusion of myometrial tissue is observed with 48-72 hours after UAE possible due to the rich collateral supply in the pelvis (Scheurig-Muenkler *et al.* 2010). Further, the vasculature of the leiomyoma tissue may be different from that of the myometrium as suggested by the gradual reversal of myometrial ischaemia. It is likely that at the time of maximum postprocedural pain, the myometrial ischaemia was most severe, while leiomyoma ischaemia was complete and mainly irreversible.

The use of a large volume of embolic agent was associated with severe postprocedural pain. Volkers et al. also demonstrated a distinct correlation between high pain scores and the amount of PVA particles (Volkers *et al.* 2006).

The finding that postprocedural pain cannot be predicted based on baseline uterine or leiomyoma volume is in concordance with findings by Roth et al. (Roth *et al.* 2000). Nor the embolisation of both uterine arteries to complete stasis was associated with the severity of pain.

***Determinants of Uterine Ischaemia***

Although most investigators have found normal perfusion of the myometrium at mid- and long-term follow-up MRIs, some case reports have described uterine necrosis after UAE (Godfrey *et al.* 2001, Torigian *et al.* 2005). Therefore, we also evaluated possible determinants of the myometrial and leiomyoma ischaemia. Our results imply that the infarction of leiomyomas can be achieved by embolising to full stasis, which often requires a considerable amount of microspheres. Indeed, the volume of embolic agent correlated positively with the leiomyoma ischaemia. On the other hand, embolisation of both uterine arteries to complete stasis was not associated with the severity of myometrial ischaemia. Further, Scheurig-Muenkler et al. observed that transient uterine ischaemia regularly occurred after UAE even with the use of a limited embolisation technique (Scheurig-Muenkler *et al.* 2010). It is notable that the attempted endpoint of microsphere administration in our study was near-stasis of the uterine artery, but in reality stasis was complete in almost one-half of the arteries.

The apparently paradoxical finding that the use of a small volume of embolisation agent and smaller uterine corpus were associated with more severe myometrial ischaemia probably reflects the difficulty in deciding the proper time point of stopping microsphere administration, especially in the case of a small uterus. In other words, because in small uteri also the capacity of leiomyomas to intake microspheres is very limited, even a small amount of embolic agent can cause myometrial ischaemia. Thus, small uteri may be less suitable targets for UAE.

These findings raise the question whether a more selective embolisation technique or a technique with an earlier endpoint

than "stasis or near stasis" could result in a therapeutic effect with fewer side effects. The definition of endpoint based on DSA is intrinsically subjective (Lewandowski *et al.* 2007). The contrast enhanced ultrasound could be useful to detect the lack of leiomyoma perfusion indicating the optimal amount of embolic agent and the optimal endpoint of embolisation. In addition, a combined CT and angiography suite would also provide more objective means of verifying the lack of perfusion. In future, intraprocedural MRI in interventional MRI suites might be a feasible option for this without a radiation exposure. Currently, however, effective postprocedural pain relief should be available until the selection of the optimal endpoint of embolisation, and the optimal type, size and amount of the embolisation agent are clarified.

The repeatability of evaluation of ischaemia was good, implying that the visual analysis of the severity and percentage of the leiomyoma and myometrial ischaemia is a useful method for clinical diagnostics. Pelage et al. used similar visual analysing of percent ischaemia of leiomyomas at dynamic sequence (Pelage *et al.* 2004).

We used VRS for assessing the postprocedural pain intensity. It has proven to be as valid, reliable and appropriate for use in clinical practice as the Visual Analogue Scale and the Numerical rating Scale (Williamson *et al.* 2005). A review of these three commonly used pain rating scales concluded that the VRS is the least sensitive tool of the three, but it is easy to use, while the VAS has the highest failure rate (Williamson *et al.* 2005).

***Limitations of Study III***

Because the first postprocedural MRI after UAE was not done at the time of maximum postprocedural pain, the study provides only indirect evidence that myometrial ischaemia is the main determinant of postprocedural pain. On the other hand, it is clear that performing MRI at the time of severe postprocedural pain is very challenging or even impossible. Further, our analysis does not address other possible causes of

postprocedural pain, such as ovarian and muscle ischaemia as a result of inadvertent embolisation. Further, in the study protocol, nondynamic delayed gadolinium- enhanced sequences were obtained with single phase imaging 90 seconds after contrast agent injection. The presence of non-enhancing tissue at this time point indicates that there has not been detectable perfusion in the earlier stages either.

## 6.4 VALUE OF QUANTATIVE MRI MEASUREMENTS IN PREDICTING UTERUS AND LEIOMYOMA SIZE REDUCTION AFTER UAE (STUDY IV)

According to the results of Study IV, the extent that UAE will reduce the sizes of the uterus and dominant leiomyoma can be predicted by simple analysis of preinterventional MRI parameters. We selected the leiomyoma and uterine size as outcome variables because they can be measured accurately by MRI. Further, the limited size reduction after procedure has been shown to be associated with clinical failure and recurrent symptoms (Goodwin *et al.* 1999, Lohle *et al.* 2008, Pelage *et al.* 2004). Further, Study I demonstrated that leiomyoma volume and uterine dimensions in pre-MRI are associated with pressure symptoms validating the feasibility of the results.

### *Leiomyoma-to-skeletal Muscle-ratio*

In the study, the best predictor of leiomyoma and uterus size reduction proved to be the leiomyoma-to-skeletal muscle SI-ratio derived from T2-weighted images. Thus, leiomyoma size reduction was highest in patients with high signal in T2-weighted images. In three previous studies, the SI of leiomyomas were assessed visually and compared with those of skeletal muscle and myometrium (Burn *et al.* 2000, deSouza *et al.* 2002, Harman *et al.* 2006): the authors also found that a leiomyoma SI higher than that of skeletal muscle in T2 images was predictive of a good response to UAE. Using numeric values to characterize leiomyoma, instead of visual

dichotomized variable, allowed us to identify continuum in the relationship between SI and size reduction. Namely, leiomyomas with SI three or four times higher than that found in skeletal muscle underwent the highest size reductions compared to leiomyomas only two times higher SI.

Histopathological basis for the low SI in T2- weighted images has not been fully clarified. The results imply that a low SI is associated with increased degeneration. However, this notion contrasts with findings by Yamashita et al. who found that degenerated leiomyomas had higher signal in T2-weighted images and that their response to gonadotropin-releasing hormone analog was minimal (Yamashita *et al.* 1993). In recent studies with MRI-guided focused ultrasound, leiomyoma size reduction was smallest in leiomyomas with high SI in T2-weighted images as well (Funaki *et al.* 2007, Lenard *et al.* 2008). Accordingly, it is possible that there are other factors than degeneration (possibly cellularity) that explain these variable results.

Image analysis was straightforward and consisted of two ROIs drawn in a PACS system. Such measurement is feasible for routine clinical work, because the same MRI sequencies can be used to study uterus anatomy and size and location of the leiomyoma.

***T1 Time***

Our finding that the long T1 time, i.e. low SI in T1-weighted images, predicted the ability of UAE to reduce uterus and leiomyoma sizes might be explained by a low concentration of free proteins due to the presence of nondegenerated leiomyomas. Similarly, three studies (Burn *et al.* 2000, Harman *et al.* 2006, Jha *et al.* 2000) found that leiomyomas with SI higher than that of myometrium or skeletal muscle in T1-weighted images were predictive of a poor response to UAE.

In the study, the imaging for T1 time was performed by changing the inversion time manually; however, newer scanners are able to measure T1 times automatically. Using the T1 time for predictions provides advantages over using the leiomyoma-

to-muscle T2 SI-ratio. First, the T1 time is measured only from the leiomyoma, thus, the properties of fat between skeletal muscle bundles do not influence the T1 time measurement. In addition, modifications in sequence technology do not affect the results of T1 time measurements because T1 time is an absolute value. In contrast, T2 SI-ratios are relative and may be influenced by equipment and technical imaging parameters.

***Contrast Enhancement***

In our study contrast enhancement was valuable in identifying patients with ≥50% uterus size reductions. Hypervascular leiomyomas have been shown to have a greater reduction in vascularity than hypovascular leiomyomas (Jha *et al.* 2000). Histologically, increased contrast enhancement is associated with high cellularity, increased vessel density, and low degeneration, measured as hyalinization (Yamashita *et al.* 1993). Contrast enhancement could be a useful parameter in leiomyomas that are hyperintense in T2 images due to degeneration and show no enhancement due to necrosis. Actually, nonenhancing leiomyoma has been used to preclude UAE (Nikolaidis *et al.* 2005). The value of contrast enhancement imaging in the present study was controversial. In Spearman rank correlation analysis contrast enhancement was not associated with leiomyoma size reduction. This result is supported by two previous studies (Burn *et al.* 2000, deSouza *et al.* 2002).

***Limitations of Study IV***

We did not correlate MRI findings with histopathological characteristics. Further, multiphase or dynamic first-pass perfusion imaging with absolute perfusion quantification could possibly provide more comprehensive data of the value of leiomyoma blood perfusions in the prediction of the UAE results, as shown in patients treated with gonadotropin-releasing hormone (Okuda *et al.* 2008).

## 6.5 UTERINE ARTERY EMBOLISATION FOR LEIOMYOMAS IN CURRENT CLINICAL PRACTICE

At the time of the start of this study, promising short-term results of UAE in treating leiomyomas were reported. Recently, as long as 5-year follow-up trials have been carried out (Lohle *et al.* 2008, Spies *et al.* 2005c, van der Kooij *et al.* 2010). Our results confirm the previous findings from the other randomised trials: UAE is a valuable therapeutic option alternative for surgery in women with symptomatic leiomyomas. UAE is no longer considered as an experimental treatment for leiomyomas. UAE is currently accepted and considered a safe and effective treatment for symptomatic women with uterine leiomyomas (ACOG 2008, Joffre *et al.* 2004, Lohle *et al.* 2008, Pron *et al.* 2003a, Pron *et al.* 2003b, Pron *et al.* 2003c, Pron *et al.* 2005, Pron *et al.* 2003d, Pron *et al.* 2003e, Spies *et al.* 2005c, Spies *et al.* 2007, Walker *et al.* 2006b, Walker *et al.* 2002, van der Kooij *et al.* 2010, Watson *et al.* 2002, Volkers *et al.* 2007). The minimally invasive nature of the procedure, along with low morbidity, rapid recovery, high success rates and the psychological advantage of an organ-preserving treatment make UAE an attractive alternative to surgical treatments.

Hysterectomy is the most common surgical treatment for leiomyomas in Finland, possibly due to cultural aspects to perform traditionally hysterectomy for the symptomatic women who have completed childbearing. However, in recent years, the rate of hysterectomies for leiomyomas has reduced. Recently, the Finnish Office for Health Technology Assessment (Finnohta) has made the recommendations for UAE in treating symptomatic uterine leiomyomas. This systematic literature search and evaluation by the group of Managed Uptake of Medical Methods concluded that UAE is a safe, clinically effective and cost-effective method as an alternative for hysterectomy (Hippeläinen M 2011). However, despite the growth of favourable outcome information, many gynecologists do not routinely offer UAE as an alternative to hysterectomy. A recent prospective study revealed that failure to fully disclose

alternative minimally invasive treatment options may result in patient dissatisfaction due to the fact that many patients do not wish to have any surgery (Zurawin *et al.* 2010). In addition, in a recent study of the clinical practise of UAE showed that although UAE is widespread in Europe, the overall numbers of UAE procedures seems to be rather low (Voogt *et al.* 2010). Thus, the good collaborative relationship and open communication between the gynecologist and interventional radiologist facilitates leiomyoma treatment tailored according to the carefully considered requests of individual patients.

A recent article by Goodwin and Spies reviews the clinical recommendations for UAE (Goodwin *et al.* 2009). UAE is a reasonable treatment option for most patients in whom UAE has no contraindications. There are some important contraindications to UAE, including pregnancy, pelvic cancer, active infection, and some endometrial or adnexal abnormalities requiring further treatment (Goodwin *et al.* 2009). Thus, a careful pre-embolisation evaluation both clinically and with imaging together with appropriate technical expertise in embolisation is important to effectively treat leiomyoma patients. Although pregnancy is possible after embolisation, existing data suggest better reproductive outcomes for myomectomy in the first 2 years after UAE (Freed *et al.* 2010, Goodwin *et al.* 2009, Mara *et al.* 2008). Further, there is some data that patients with very large leiomyomas and uteri may have less satisfaction with the clinical results of UAE (Goodwin *et al.* 2009, Spies *et al.* 2002b).

Significant registry in this field, The Fibroid Registry for Outcomes Data for Uterine Embolisation (FIBROID) was created in 1999 (Goodwin *et al.* 2008, Myers *et al.* 2005, Spies *et al.* 2005b, Worthington-Kirsch *et al.* 2005). The results have demonstrated that UAE results in a durable improvement in quality of life when performed by an experienced interventional radiologist (Goodwin *et al.* 2008). Further, SIR has created standards of practise for UAE including training, reporting, quality assurance, and clinical care (Andrews *et al.* 2004, Andrews *et al.* 2009, Goodwin *et al.* 2003, Goodwin *et al.* 2001, Hovsepian *et al.*

2004, Hovsepian *et al.* 2009, Spies *et al.* 2001c, Stokes *et al.* 2010). A disease-specific symptom and health-related quality of life questionnaire for leiomyomas, i.e. UFS-QOL, was developed as part of the FIBROID Registry for the evaluating the severity of symptoms before and after UAE (Spies *et al.* 2002c). UFS-QOL would be a feasible tool particularly for comparing different treatment options for leiomyomas. However, our study started before publishing the questionnaire.

## 6.6 FUTURE PERSPECTIVES

The long-term (3-year) follow-up MRI and the clinical success as well as the SF-36 forms of our prospective study population should be analysed because UAE for leiomyomas has not been applied widely in Finland. Comparison between UAE and other uterine conserving procedures with longer follow-up is needed.

It is an extremely important issue to clarify whether MRI has value to select patients to UAE. There is no accurate recommendation what kind leiomyomata uteri should or should not be treated with UAE. In this study we concluded that we can predict the extent that UAE will reduce the sizes of the uterus and dominant leiomyoma at 6-month follow-up by preinterventional MRI parameters. Thus, correlation study of the 3-year clinical outcome with the preinterventional MRI findings is warranted. Finally, the type and amount of embolic agent continues to be a matter of debate.

Future studies should focus on analysing quantitatively the absolute perfusion of leiomyomas and myometrium after UAE, and try to find out if any perfusion parameters have prognostic significance for long-term success, and if there will be any negative long-term influences in perfusion of normal myometrium tissue.

## 6.7 ETHICAL ASPECTS

All study patients had symptoms that required treatment, and the severity of symptoms warranted consideration of hysterectomy. The patients were provided written information about the study (approved by ethics committee) as well as the aims of the study. They also were given explanations about the interventions, the sedation and anaesthesia needed. The risks, benefits, and possible complications of UAE as a rather new treatment were described. Further, they also were given the opportunity to ask questions and time to consider participation. The informed written consent was obtained from patients.

Before the initialising of this study, UAE was accepted and widely utilized for post-partum hemorrhage, postoperative bleeding, and arteriovenous malformations (Abbas *et al.* 1994, Korhonen *et al.* 2010). Further, the initial results of UAE for leiomyomas were promising and the rate of major complications very low in previous studies.

All UAE interventions were performed by highly experienced interventional radiologist, and hysterectomies were performed as close of well-established daily practice as possible by an experienced gynecologist. Concerning the postprocedural pain after UAE and hysterectomy the patients were provided with effective pain relief with intravenous opioids when needed.

# 7 Conclusions

1. In comparison with pressure symptoms, menorrhagia is associated with a submucosal leiomyoma largely protruding into the cavity, smaller uterine and leiomyoma size, and with more intense contrast enhancement on MRI. The large leiomyoma and uterine size contribute to increased urinary frequency, whereas other mechanisms for urinary stress incontinence and pain symptoms should be considered.

2. UAE is an effective and safe treatment option for women with symptomatic leiomyomas in a mid-term follow-up. Concerning with patient selection, UAE may be a preferable treatment over hysterectomy especially for women with a feeling of pressure. UAE is associated with faster recovery, but with an increased number for secondary interventions. Even then, UAE is not inferior to hysterectomy concerning patients' satisfaction.

3. Postprocedural pain after UAE is a frequent adverse effect and it is often severe. This pain is related to the pathophysiological process of myometrial ischaemia caused by effective embolisation and to the use a large amount of embolic agent.

4. The extent that UAE will reduce the size of the uterus and the dominant leiomyoma can be predicted by preinterventional MRI parameters, i.e. the leiomyoma- to-skeletal muscle T2 SI-ratio and T1 time of the dominant leiomyoma.

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**Anu Ruuskanen**

# *Uterine Artery Embolisation for Leiomyomas*

*Magnetic Resonance Imaging Studies and a Randomised Prospective Comparison with Hysterectomy*

Uterine artery embolisation (UAE), new treatment for uterine leiomyomas has been developed to substitute for major surgery. This randomised study comparing UAE and hysterectomy confirmed that UAE is a safe and effective treatment for symptomatic leiomyomas. In addition, this thesis observed that post-UAE pain is often severe and is partly explained by myometrial ischaemia on 24-hour magnetic resonance imaging (MRI) and large volume of embolic material. MRI measures can also be used to predict uterus and leiomyoma size reduction after UAE. Moreover, preinterventional MRI findings of uterine leiomyomas give objective anatomical base for symptoms of leiomyomata patients.

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