Clinical aspects of uterine artery embolization

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GENERAL DISCUSSION
AND SUMMARY
General discussion

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

Technique of uterine artery embolization

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

Results on follow-up

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

**Contra-indications for uterine artery embolization**

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

**Future perspectives**

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

In Chapter 1 a general introduction is provided.

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

In Chapter 3 the efficacy and safety of precisely calibrated microspheres used for UAE in women with symptomatic uterine fibroids is evaluated. Between August 2006 and August 2008, 86 consecutive premenopausal women were treated with UAE. Embolization was performed via a bilateral femoral approach using two microcatheters. Calibrated microspheres of 500, 700 and 900 µm alone or in combination were used as embolic agent. MRI was used to assess the change in uterine and dominant fibroid volume as well as dominant fibroid and overall infarction rate. Clinical follow-up was evaluated by the Uterine Fibroids Severity and Quality of Life questionnaire (UFS-QOL) at baseline, at 3 months and in November 2008 after a mean follow-up of 12.8 months. The UFS-QOL showed significant improvement in both symptom severity and quality of life after 3 months and continued to improve at last follow-up of mean 12.8 months.

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

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

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

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

In Chapter 7 we retrospectively assessed the complications and outcomes of UAE in 29 women with 31 pedunculated fibroids in a large single center patient cohort. MRI prior to embolization and at 3 months was used to calculate stalk diameter change and volume reduction of both pedunculated fibroid and uterus. Complications were recorded and long-term clinical follow-up (mean 33 months) was assessed by a questionnaire.

Mean uterine and pedunculated fibroid volume reduction was 37% and 33%. Mean stalk diameter reduction was 0.3 cm or 13% from initial mean diameter. Stalk enhancement was not affected by UAE. Mean pedunculated fibroid infarction and mean overall infarction rate were for observer 1; 87% and 92% and for observer 2; 88% and 92% with good inter-observer variability. All women returned the questionnaire and no early or late complications of UAE were reported. In this small series of pedunculated subserosal fibroids treated with UAE, no complications occurred. Our findings suggest that treatment of pedunculated fibroids with UAE may be safe and effective.

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