Uterine artery embolization versus hysterectomy for symptomatic uterine fibroids

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UTERINE ARTERY EMBOLIZATION **VERSUS** HYSTERECTOMY FOR SYMPTOMATIC UTERINE FIBROIDS

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UTERINE ARTERY EMBOLIZATION **VERSUS** HYSTERECTOMY FOR SYMPTOMATIC UTERINE FIBROIDS

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Chapters 7 and 9 will be defended by W.J.K. HEHENKAMP
Chapters 3 and 13 will be defended by N.A. VOLKERS
All other chapters will be defended by both authors

1 INTRODUCTION & OUTLINE

GENERAL INTRODUCTION

This thesis describes the results of a randomized trial comparing two treatments for symptomatic uterine fibroids: uterine artery embolization (UAE) and hysterectomy. The general introduction discusses the background and rationale of the trial and provides an overview of the epidemiology, symptomatology and treatment of uterine fibroids.

UTERINE FIBROIDS

Uterine fibroids or (leio-) myomas are benign tumors resulting from the neoplastic transformation of a single smooth muscle cell of the uterus [1]. Although the cause of uterine fibroids is far from clear, a genetic predisposition is most likely and several genes, which are possibly involved in the development of fibroids, have been identified [2].

Fibroids may arise throughout the body (e.g. from smooth muscle cells in arterioles found in the lung or other organs), but most commonly present in the uterus, ranging in size from several millimeters to more than 20 centimeters. Uterine fibroids are often categorized according to their location: intramural fibroids are located within the myometrium (most common); submucosal fibroids protrude into the uterine cavity; subserosal fibroids are located beneath the serosa; cervical fibroids are located in the cervix.

EPIDEMIOLOGY

Most women with symptomatic fibroids are in their 30s and 40s. Symptoms related to uterine fibroids usually subside after the onset of menopause, when menstrual cyclicity and steroid hormone levels decrease. The lifetime risk of developing one or more uterine fibroids during reproductive life is estimated to be approximately 25% [3], but the prevalence has been reported to range from 5.5% to 77% [4;5].

Several risk factors for the development of uterine fibroids have been identified. An increased risk was found to be associated with the black race [6-8], nulliparity [9;10], early menarche (< 11 years of age), [11] and a high body mass index [6;12-14]. A reduced risk was associated with parity (prior pregnancy) [11;15], a late last pregnancy [13], a high number of pregnancies [11-14], current contraceptive use [6;15], and current smoking [10;13;16].

SYMPTOMATOLOGY

The majority of fibroids are small and asymptomatic. Some fibroids, however, cause significant problems interfering with women's quality of life and may warrant treatment. The severity of symptoms is related to the number, size and location of the fibroids [17].

Abnormal menstrual bleeding (menorrhagia and/or metrorrhagia) is the most common symptom (approximately 30%) causing women with uterine fibroids to seek medical care [3]. The exact mechanism by which fibroids cause increased menstrual blood loss is largely unknown, although several theories have been postulated. The fibroids might obstruct the veins in the myometrium, thereby causing venous congestion and dilatation of the endometrial veins, leading to prolonged bleeding and perhaps impairment of normal hemostatic mechanisms. Submucosal fibroids have been thought to cause increased bleeding as a result of endometrial ulcerations developing over the fibroid mass. Another theory states that uterine fibroids may dramatically increase the surface area of the endometrium, thereby increasing menstrual loss [3;18]. Normal uterine contractility, which presumably plays a role in controlling uterine bleeding, may be impaired by uterine fibroids, thus explaining menorrhagia [3;19]. More recently, dysregulation of several growth factors and their receptors has been suggested to play a role affecting vascular function and angiogenesis. These changes may be responsible for vascular malfunction, thus causing menorrhagia [20].

Heavy menstrual loss may be responsible for associated problems, such as iron deficiency anemia, social embarrassment, and absence from work.

Lower abdominal pain is also associated with uterine fibroids. Pelvic pain may occur both during and in-between menstrual periods. Posterior fibroids may cause lower back pain, whereas those found in the broad ligament may cause unilateral lower abdominal pain or may compress the sciatic nerve [17]. Sometimes acute pain may arise from spontaneous fibroid necrosis or torsion of a pedunculated fibroid [21].

The pelvic and abdominal discomfort experienced by women with fibroids is often referred to as 'pressure' or 'bulk' symptoms. The fibroid uterus is irregularly shaped and causes specific symptoms due to the pressure from fibroids in particular locations (i.e. increased urinary frequency, urinary incontinence, constipation). Rarely, ureteric compression by the enlarged fibroid uterus at the pelvic brim, may lead to uni- or bilateral hydronephrosis [3].

The role of uterine fibroids as a causal factor in infertility remains controversial. The incidence of both fibroids and infertility increases with age and may co-exist by mere chance [17]. Fibroids are common and occur in both fertile and infertile women alike, and there is no evidence that the mere presence of fibroids causes infertility, with the exception of pedunculated fibroids impinging the uterine cavity [21].

The incidence of uterine malignancies in patients with presumed fibroids is reported to be 0.23% to 0.49% [22;23]. In the past, the speed of fibroid growth was considered to be a risk factor for transition to leiomyosarcoma, especially when tumor growth was rapid. This view was not confirmed in later research [17;22]. However, the risk of uterine malignancies increases with age, and any growth of presumed fibroids after menopause should raise suspicion and needs proper evaluation [22].

TREATMENT OF UTERINE FIBROIDS

UTERUS SPARING TREATMENT OF UTERINE FIBROIDS

Despite the high incidence of fibroids and the large number of women being treated, considerable uncertainty and controversy remains among both clinicians and patients regarding the optimal management of symptomatic fibroids. Treatment choices depend on several factors, e.g. severity of symptoms, age of the patient, location of fibroid(s), patient's preference and physician's preference, experience, and skills. In general, non-invasive therapies, i.e. oral contraceptives, progestins, coagulation stimulants, GnRH-analogues and non-steroidal anti-inflammatory drugs are considered to be the first line treatments, together with the hormone-releasing intra uterine system which may offer symptomatic relief. Hysteroscopic resection of is a very successful minimal invasive treatment, which can be performed only in case of (pedunculated) submucosal myoma's, which are reached transcervically from within the uterine cavity [24]. Transabdominal myomectomy is an option when fibroids are limited in number and localized mostly subserously or in the uterine wall. Myomectomy is reserved for those patients with symptomatic fibroids who still wish to conceive [25].

When other therapies are not an option or provide unsatisfying results, a hysterectomy offers the final solution for symptomatic relief.

HYSTERECTOMY

Hysterectomy is the most common non-pregnancy related surgical procedure in women [26-30]. Hysterectomy rates vary over the years and differ significantly among countries [31]. The highest incidence of hysterectomies is reported for women aged between 40 and 50 years [26]. In the Netherlands approximately 16000 hysterectomies are performed each year, including those for uterine fibroids [32]. According to the literature, approximately 1/3 of hysterectomies are carried out for uterine fibroids (ranging from 26-34%) [26;27;33;34], although even higher

proportions have been reported: 40% [21], 48% [9] and 54.6% [30]. Thus, in the Netherlands approximately 5000 hysterectomies per year are being performed for uterine fibroids.

Abdominal hysterectomy is the most commonly performed procedure in patients with uterine fibroids, mainly because of the easy access provided by this approach in women with enlarged uteri.

Complications after hysterectomy performed for benign indications are relatively common and range between 9-17% for abdominal hysterectomy [35-37]. Major complications, however, are rare (~1% [37;38]). Recently, however, one large randomized trial reported a major complication risk of 6.2% for abdominal hysterectomy [39]. Mortality rates after hysterectomy are low and range from to 0.06 [40] to 0.38% [37]. Quality of life improves significantly after hysterectomy [39;41] and satisfaction rates are around 95% [42-44].

Drawbacks of hysterectomy are an increased risk of earlier menopause with the associated symptoms [45-47], increased risk of developing urinary incontinence at age > 60 [48], and possibly a decreased body image [49].

UTERINE ARTERY EMBOLIZATION

A possible alternative to hysterectomy is uterine artery embolization (UAE), which was introduced in 1995 [50]. UAE as a technique has been used for over 20 years especially in the treatment of massive, uncontrollable bleeding from trauma [51], postpartum hemorrhage [52;53] and ectopic pregnancy [54]. In the early 1990's, Ravina et al. started using embolization as a pre-surgical intervention to decrease intra-operative bleeding during fibroid surgery [55]. However, the embolization resulted in a subsiding of symptoms and patients no longer needed additional surgery. So, the use of embolization as a primary therapy for fibroid disease was a serendipitous discovery.

UAE is performed by an interventional radiologist. The treatment takes place under conscious sedation or epidural anesthesia. A percutaneous catheter is introduced into the femoral artery using either a unilateral or bilateral technique and manipulated under fluoroscopic guidance into the uterine arteries. When the catheters are in place the embolization is carried out, using polyvinyl alcohol (PVA) particles, PVA microspheres or gelatin-coated tris-acryl polymer micropsheres, which are injected into both uterine arteries, thus reducing or occluding uterine blood flow at the arteriolar level. This causes irreversible ischemic injury to the fibroids while avoiding permanent damage to the uterus. Deprived of the arterial blood supply, the fibroids will shrink and symptoms will subside.

Since the first case series was published [50], several other uncontrolled small series followed [56-60]. Overall, these case series showed a short term reduction of menorrhagia and bulk or pressure symptoms between 80% and 90% of patients and mean fibroid volume reduction

from 50% to 60%. The early papers on UAE have claimed that many women with an indication for hysterectomy, would be better off by undergoing UAE [61;62].

THE CLINICAL PROBLEM

Since hysterectomy is considered to be a major surgical procedure with a long recovery time and possible long term sequelae, new alternative treatments such as UAE should be evaluated in a randomized controlled trial to determine their place in the treatment of symptomatic uterine fibroids. In the absence of effectiveness data from randomized controlled trials, implementation of UAE as a standard treatment option in the Netherlands was undesirable in our view (www.nvog-documenten.nl: 'leidraad introductie nieuwe technieken en methoden'). Therefore the EMMY trial was set up to evaluate UAE for the group of patients with the worst symptomatology: those who had no other treatment option left than a hysterectomy.

STUDY AIM

The aim of this study was to evaluate the safety and clinical effectiveness of UAE in comparison to hysterectomy, the standard treatment of therapy resistant uterine fibroids,
within a time frame of two years.
The specific research questions of the EMMY trial were:

1. Is UAE non-inferior to hysterectomy defined as: the elimination of menorrhagia in at least 75% of UAE patients, in whom consequently a hysterectomy can be avoided?
2. How do UAE and hysterectomy compare in terms of peri-procedural and short term follow up characteristics, major and minor complications, duration of hospital stay, and recovery time?
3. Do general and disease-specific Health Related Quality of Life differ between UAE and hysterectomy?
4. Is there a difference between UAE and hysterectomy in the impact on ovarian function?
5. Is UAE cost effective in comparison to hysterectomy?
6. Which treatment option do patients prefer?
7. What is the validity and reproducibility of various diagnostic tools used in this trial?

These questions will be addressed in the following chapters of this thesis.

OUTLINE OF THE THESIS

PART I: SHORT TERM RESULTS

CHAPTER 2 describes the general methodology of the trial. Furthermore, this chapter presents the complication rates during hospital stay until 6 weeks follow up, as well as short term resource use (hospital stay, unscheduled visits and re-admissions).

CHAPTER 3 discusses technical results of UAE, anatomic variations of the uterine artery and possible risk factors for technical UAE success/failure and other complications of the procedure.

CHAPTER 4 evaluates post-procedural pain, together with time to resume daily activities, i.e. work, household activities and doing groceries between the two treatment options.

CHAPTER 5 focuses on a special case of fibroid expulsion 3 months after the UAE treatment.

PART II: LONG TERM RESULTS

CHAPTER 6 describes the clinical results at 24 months follow up: clinical failures of UAE, re-interventions, menstrual bleeding characteristics, effect on pain- and bulk-related complaints and reduction of uterine and fibroid volume.

CHAPTER 7 describes the impact on ovarian function and reserve by assessing several hormonal parameters as well as menopausal symptoms within and between groups.

CHAPTER 8 analyses different aspects of health related quality of life, assessed by various validated questionnaires, as well as patients' satisfaction.

CHAPTER 9 compares the impact of both treatments on sexual functioning and body-image by means of validated questionnaires.

CHAPTER 10 presents a detailed cost-effectiveness analysis. The analysis includes in-hospital costs as well as societal costs outside the hospital.

CHAPTER 11 elaborates on the treatment burden and patients' treatment preferences prior and after treatment.

PART III: VALIDATION AND RELIABILITY STUDIES

CHAPTER 12 describes the impact of randomization on Health Related Quality of Life (HRQOL). HRQOL is compared between the randomized group that participated in the trial, and those eligible patients who refused trial participation before and 1 year after therapy.

CHAPTER 13 validates uterine fibroid characteristics rendered by MRI measurements. An intra- and interobserver study is presented for important UAE parameters, such as size, location and number of uterine fibroids.

CHAPTER 14 contains a comparison between bimanual estimation of uterine size and ultrasound measurements and the actual weight of the uterus at hysterectomy, as reported during histopathologic examination. Furthermore ultrasound and bimanual examination are compared with MRI measurements.

PART IV: SUMMARY, GENERAL DISCUSSION AND CONCLUSION

CHAPTER 15 summarizes all our results categorized by subject. Furthermore we discuss the results from the EMMY trial in the context of current literature. Finally our conclusions are postulated.

CHAPTER 16 provides a summary, general discussion and conclusions in Dutch.

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UTERINE ARTERY EMBOLIZATION **VERSUS** HYSTERECTOMY FOR SYMPTOMATIC UTERINE FIBROIDS

I

SHORT TERM RESULTS

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UTERINE ARTERY EMBOLIZATION VERSUS HYSTERECTOMY IN THE TREATMENT OF SYMPTOMATIC UTERINE FIBROIDS (EMMY TRIAL): PERI- AND POST PROCEDURAL RESULTS FROM A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective

A randomized controlled trial to evaluate the safety of uterine artery embolization (UAE) compared to hysterectomy.

Methods

Twenty-eight Dutch hospitals recruited 177 patients with symptomatic uterine fibroids and menorrhagia, who were eligible for hysterectomy. Patients were randomized to UAE (n=88) or hysterectomy (n=89). In this paper we evaluate the peri- and post procedural complications, length of hospital stay, unscheduled visits and readmission rates up to 6 weeks post intervention. Analysis was by intention to treat.

Results

Bilateral UAE failure occurred in 4 patients (4.9%). Major complications occurred in 4.9% (UAE) and 2.7% (hysterectomy) of cases (p=0.68). The minor complication rate from discharge until 6 weeks after was significantly higher in the UAE group than in the hysterectomy group, (58.0% vs. 40.0%; RR: 1.45 [1.04-2.02]; p=0.024). UAE patients were more often readmitted (11.1% vs. 0%; p=0.003). Total length of hospital stay was significantly shorter in UAE patients (mean [SD]: 2.5 [2.7] vs. 5.1 [1.3]; p<0.001).

Conclusion

UAE is a procedure with a low major complication rate similar to hysterectomy and with a reduced length of hospital stay. Higher readmission rates after UAE stress the need for careful post-procedural follow-up.

INTRODUCTION

Uterine artery embolization (UAE) for the treatment of heavy menstrual bleeding caused by uterine fibroids was first described in 1995 [1]. Since then several large case series have been published describing the risks and benefits of UAE [2-6]. These reports suggest that UAE may have advantages over surgery, but are hampered by the inclusion of patients with strong treatment preferences and the lack of a control group. Obviously, this seriously affects the validity and generalizability of their results.

To evaluate the safety and efficacy of UAE in comparison to the standard treatment, i.e. hysterectomy, we initiated a prospective, multi-center, randomized controlled trial comparing UAE with hysterectomy for the treatment of menorrhagia caused by uterine fibroids. In the trial, patients are being followed until 2 years after the intervention. In this report we present the baseline and procedural characteristics, peri- and post procedural complications, duration of hospital stay, unscheduled visits and readmissions up to 6 weeks post intervention.

METHODS

STUDY DESIGN

The EMMY (EMbolization versus hysterectoMY) study is a multi-center, randomized controlled trial, conducted in the Netherlands. Five university hospitals and 29 general hospitals participated in the trial. Patients visiting the gynecological outpatient clinics were asked to participate if they met the following criteria: 1) the clinical diagnosis of uterine fibroids had been confirmed by ultrasonography, 2) menorrhagia, (subjectively reported by the patient as increased or prolonged menstrual blood loss which causes dysfunction in daily life), was their predominant complaint, among other possible fibroid related signs and symptoms, 3) they were premenopausal and 4) they were to be scheduled for a hysterectomy. Whenever other treatment options were still available, women were not asked to participate, but were treated otherwise.

Women were excluded if: 1) preservation of the uterus was warranted for future pregnancy, 2) renal failure (kreatinine $>$ 150 mmol/L), active pelvic infection or clotting disorders were clinically established, 3) they were allergic to contrast material, 4) uterine malignancy was suspected, 5) submucosal fibroids with 50% of their diameter within the uterine cavity or dominant pedunculated serosal fibroids were present.

After written informed consent had been obtained the attending gynecologist contacted the trial bureau by telephone, where the patient was registered and randomly assigned (1:1) to

UAE or hysterectomy, using a computer-based minimization scheme ('balancing procedure'), stratified for study center. The randomization result was recorded electronically.
According to Dutch guidelines the study was approved by the Central Committee Involving Human Subjects (www.ccmo.nl) and by local ethics committees of participating hospitals.

PRE-ASSESSMENT

All clinical data were prospectively recorded in a standardized case record form during the entire study period. All patients underwent a pelvic ultrasound either trans-vaginally or trans-abdominally. The uterus and the largest fibroid were measured in three dimensions, i.e. longitudinal (D1), anterior-posterior (D2), and transverse (D3). Volumes were calculated using the formula (D1 $\times$ D2 $\times$ D3 $\times$ 0.5233) [7].

PROCEDURES

Uterine artery embolization

Patients were advised to discontinue any GnRH analogues treatment at least 1 month before the UAE [8;9]. UAE was performed in all participating hospitals. The first 2-3 procedures were supervised by an interventional radiologist (JR), with ample experience in UAE. All radiologists were experienced in intervention radiology, including various embolization techniques in general. At the start of the study UAE was not a routine procedure for all radiologists. Seven radiologists were considered experienced in UAE group (having performed $>$ 10 UAE procedures) and nineteen interventional radiologists had less experience in UAE (having performed $<$ 10 UAE procedures). Patients received an intravenous line and a Foley catheter prior to UAE. UAE was performed under local or epidural/spinal anesthesia. The use of analgesics and antibiotics was not standardized. Femoral artery access could be unilateral or bilateral. A 4-F or 5-F catheter was introduced into the femoral artery and advanced over the aortic bifurcation to the contra lateral internal iliac artery to identify the origin of the uterine artery. In case of spasm the policy was to wait, but a micro catheter and/or spasmolytics could be used within the study protocol. When catheters were placed correctly, the actual embolization was carried out. Polyvinyl alcohol particles (PVA, Contour, Boston Scientific, Beek, The Netherlands) with a size of 355-500 μm were used. Only if an anastomosis with the ovarian artery was observed 500-700 μm particles were used. PVA, mixed with contrast medium and saline, was injected into each uterine artery until parenchyma filling of the fibroids had stopped (target embolization) or until the main uterine artery was blocked with stasis of contrast (selective embolization). After the procedure groin pressure was applied for 10-15 minutes.

According to the Cardiovascular and Interventional Radiology Society of Europe guidelines UAE was considered successful whenever bilateral UAE was established; unilateral UAE was only considered a successful procedure if single-sided uterine arterial flow to the fibroids was present [10].

If a uterine artery was absent and flow to the fibroids came solely from the ovarian artery, the procedure was stopped, because of risk for ovarian damage, and considered unsuccessful. Also in case of extensive collaterals to the cervix and vaginal wall, the procedure was stopped and considered unsuccessful.

Unsuccessful procedures may not always result from the technical inability to selectively catheterize the uterine artery. Therefore, we also calculated the true technical failure rate as the total number of arteries that could be embolized (i.e. arteries were present without extensive collaterals with the cervico-vaginal vascular system), but which were not embolized because of technical inabilities to do so.

The type of anesthesia, type of UAE, the amount of PVA vials used, the amount of blood loss, the procedural complications and the duration of the procedure were recorded. After the procedure women were admitted to the gynecology ward for further care. All patients were advised to stay in hospital for at least one night. At discharge, all patients were no longer using opiates and received clear instructions on pain medication regiments. They also received written instruction with contact numbers to contact their gynecologist whenever uncontrollable pain, persistent fever or expulsion of fibroids occurred.

Hysterectomy

The type of hysterectomy and the route of access were left at the discretion of the attending gynecologist, in order to keep as close to daily practice as possible. The following procedures were allowed: abdominal hysterectomy, either by median or a pfannenstiel incision, vaginal hysterectomy, laparoscopically assisted vaginal hysterectomy and laparoscopic hysterectomy. Both supravaginal and total hysterectomies were allowed. We used no guidelines for: antibiotic prophylaxis; type of anesthesia; removal or ablation of endocervical tissue in the supravaginal hysterectomy group; concomitant adnexal surgery; wound closure; evaluation and treatment of fever; or hospital discharge criteria. Prospectively recorded were: prescription of antibiotics, type of anesthesia, type of hysterectomy, removal of the cervix, ovaries or other procedures, complications, blood loss, and duration of procedure. At discharge patients were instructed in a similar fashion as for the UAE patients.

FOLLOW-UP

Complications were classified as "major" when the events were potentially life-threatening, could lead to permanent sequelae or required surgical intervention. Other complications were listed as "minor". Nausea, pain and fever were considered "general" complications. Whenever a definite cause of fever was identified (e.g. urinary tract infection), this was listed under minor or major complications, using the criteria described above.

Complications were separately listed for two time-intervals: the hospitalization period (i.e. occurring during and after the procedure) and the first 6 weeks thereafter (i.e. between discharge and first routine visit at 6 weeks after the procedure). Complication rates were expressed as the occurrence of at least one complication within a patient and calculated for minor and major complications separately in both time-intervals and overall.

All UAE patients were routinely telephoned by the gynecologist one week after discharge to enquire about their health status.

At the first routine visit (6 weeks after the procedure) complications after discharge, unscheduled visits, readmissions and re-interventions were recorded.

SAMPLE SIZE AND ENDPOINTS

The primary endpoint of this trial was the elimination of menorrhagia after a follow-up period of two years. UAE was considered non-inferior to hysterectomy when menorrhagia resolved in at least 75% of patients [11;12], with preservation of the uterus and no significant differences in major complications between both procedures. To reject the null hypothesis that UAE and hysterectomy are not clinically equivalent (expected effectiveness of UAE = 0.875 [13-16]; expected effectiveness of hysterectomy = 0.999; threshold value $\Delta = 0.25$; $\alpha = 0.05$ (one-sided); $1\text{-}\beta = 0.90$), at least 2 x 60 (=120) analyzable patients had to be included.

The objective of the present study was to compare the following endpoints between both interventions: technical failures, procedure safety, complications, duration of hospital stay (discharge date minus procedure date) and the occurrence of unscheduled visits, re-admissions and re-interventions. For this analysis, no separate power calculation was made.

STATISTICAL ANALYSIS

All data entries were visually double checked by an independent second investigator. Analyses were done using SPSS statistical software (version 11.5.1).

Study outcomes were analyzed according to original treatment assignment (intention to treat). Differences in baseline characteristics were tested with multiple logistic regression analysis.

Differences in complications between groups were expressed in absolute numbers, rates and relative risks (RR) with 95% confidence interval (95%CI). Confidence intervals were

calculated with Statcalc (EpiInfo version 5). Differences in hospital stay were tested with the Mann-Whitney U test. Differences in categorical data were compared with χ^2-tests or Fisher Exact tests if appropriate. We also investigated the effect of experience of the radiologist and hospitals performing UAE on technical failure, complications and readmissions. A p-value of <0.05 was considered statistically significant.

RESULTS

PATIENTS

Patients were enrolled between March 2002 and February 2004. Twenty-eight of the thirty-four participating hospitals included patients. Of 349 eligible patients, 177 were randomized: 88 were allocated UAE and 89 hysterectomy (Figure 1). The majority of patients refusing participation did so for a strong preference for hysterectomy (58%) or for UAE (21%). After randomization 7 patients in the UAE group and 14 patients in the hysterectomy group refused the allocated treatment. Patients who refused the assigned treatment were comparable to participating patients in terms of: age, race, BMI, parity, symptoms and duration of symptoms (data not shown).

The mean age was 44.6 years (UAE group) and 45.4 years (hysterectomy group). Participants were predominantly white: 61.4% and 64.0% for UAE and hysterectomy respectively (Table 1).

Table 2 shows that most patients (85.3%) had already received one or more treatments for symptomatic uterine fibroids before study enrolment. Patients suffered from menorrhagia for

FIGURE 1. Trial profile

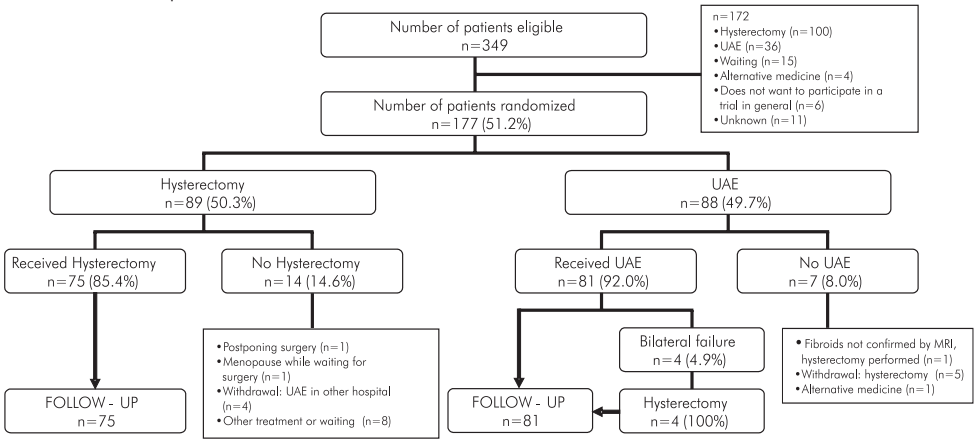

TABLE 1. Baseline characteristics: patient demographics

	UAE n=88 n (%)	Hysterectomy n=89 n (%)
Age (years)		
< 35	1 (1.1)	0 (0)
35-40	17 (19.3)	9 (10.1)
40-45	28 (31.8)	29 (32.6)
45-50	33 (37.5)	40 (44.9)
> 50	9 (10.2)	11 (12.4)
Mean (SD)	44.6 (4.8)	45.4 (4.2)
Body Mass Index (weight (kg) / length $(m)^2$)		
< 18.5	2 (2.3)	0 (0)
18.5-24.9	33 (37.5)	44 (50)
25-29.9	32 (36.4)	34 (38.6)
> 30	21 (23.9)	10 (11.4)
Mean (SD)	26.7 (5.6)	25.4 (4.0)
Parity		
0	30 (34.1)	20 (22.5)
≥ 1	58 (65.9)	69 (77.5)
Ethnicity		
Black	24 (27.3)	20 (22.5)
White	54 (61.4)	57 (64.0)
Other	10 (11.4)	12 (13.5)
Marital status		
Single	16 (18.2)	13 (14.8)
Married	55 (62.5)	54 (61.4)
Living Apart Together	5 (5.7)	4 (4.5)
Divorced	12 (13.6)	15 (17.0)
Widow	0 (0)	2 (2.3)
Employment status		
Employed	68 (77.3)	69 (78.4)
Unemployed	20 (22.7)	19 (21.6)
Smoking status		
Current smoker	21 (23.9)	23 (25.8)
Former smoker	11 (12.5)	14 (15.7)
Non-smoker	56 (63.6)	52 (58.4)
Highest educational level		*1
Elementary school	3 (3.4)	6 (6.9)
Lower vocational, lower secondary school	29 (33.0)	32 (36.8)
Intermediate and higher vocational, higher secondary school	26 (29.5)	27 (31.0)
College/University	28 (31.8)	22 (25.3)
Other	2 (2.3)	0 (0)

Data were available for all or all but 1 patient, unless stated otherwise. *1 Missing: 2
Logistic regression analysis did not reveal baseline characteristics that could predict randomization outcome

TABLE 2. Baseline characteristics: symptoms, previous treatment and uterus/fibroid characteristics

	UAE n=88 n (%)	Hysterectomy n=89 n (%)
Previous treatment		
None	11 (12.5)	15 (16.9)
Hormonal	59 (67.0)	59 (66.3)
Non-Steroidal-Anti-Inflammatory-Drugs / Tranexaminacid	45 (51.1)	41 (46.1)
Iron-supplement/blood transfusion	50 (56.8)	52 (58.4)
Surgical procedures *1	17 (19.3)	11 (12.4)
Hysteroscopic myomectomy	6 (6.8)	8 (9.0)
Laparoscopic myomectomy	0 (0)	3 (3.4)
Laparotomic myomectomy	7 (8.0)	2 (2.2)
Hysteroscopic endometrium resection	3 (3.4)	1(1.1)
Curettage	3 (3.4)	0 (0)
Symptoms		
Menorrhagia	88 (100)	89 (100)
Dysmenorrhoea	47 (53.4)	50 (56.2)
Pain (not during menstruation)	15 (17.0)	14 (15.7)
Urinary symptoms	13 (14.8)	20 (22.5)
Defecation problems	5 (5.7)	5 (5.6)
Anemia	43 (48.9)	42 (47.2)
Pressure symptoms	23 (26.1)	25 (28.1)
Other symptoms	6 (6.8)	11 (12.4)
Duration of symptoms (months)		
Median (range)	24 (3-250)	24 (4-240)
Duration of menstruation (days)		
Total days (median, range)	7 (4-28)	8 (3-42)
Heavy days (median, range)	3 (1-28)	4 (1-21)
Number of fibroids *2		
1	35 (39.8)	25 (28.1)
2	13 (14.8)	16 (18.0)
3	17 (19.3)	25 (25.8)
>3	18 (20.5)	14 (15.7)
Median (range)	2 (1-20)	2 (1-9)
Uterine volume (cm^3) *3,*5		
0-250	33 (37.9)	26 (32.5)
251-500	26 (29.9)	30 (37.5)
501-1000	19 (21.8)	16 (20.0)
>1000	9 (10.3)	8 (10.0)
Median (range)	321 (31-3005)	313 (58-3617)
Fibroid volume (dominant fibroid, cm^3) *4,*6		
0-100	55 (63.2)	41 (52.6)
101-200	14 (16.1)	20 (25.6)
201-400	11 (12.6)	12 (15.4)
>400	7 (8.9)	5 (6.4)
Median (range)	59 (1-673)	87 (4-1641)

Number of fibroids and uterine/fibroid volume were calculated by ultrasound unless stated otherwise. Data were available for all or all but 1 patient, unless stated otherwise. *1 The surgical treatments do not add up because some patients had several treatments *2 UAE missing: 5, hysterectomy missing:11; *3 UAE missing: 1, hysterectomy missing: 9; *4 UAE missing: 1, hysterectomy missing: 11; *5 MRI measurements were used in 5 patients (*6 1 patient) in the UAE group because of missing ultrasound data

TABLE 3. Procedural characteristics

	UAE n=88 n (%)	Hysterectomy n=89 n (%)
Type of UAE		
Target embolization *		-
Left uterine artery	65	
Right uterine artery	59	-
Selective embolization *		-
Left uterine artery	8	
Right uterine artery	12	-
Type of hysterectomy	(n=4)	
Abdominal hysterectomy	(2)	63
Pfannenstiel incision	(1)	50
Median incision	(1)	13
Vaginal hysterectomy	(1)	8
Vaginal hysterectomy with morcellator	(1)	1
LH with morcellator	-	2
LAVH	-	1
Cervix		
Conservation of cervix	(2)	22
Other procedures		
Removal of hydrosalpinx	-	1
Adhesiolysis	(1)	-
Salpingo-oophorectomy		
Unilateral	(1)	2
Bilateral	-	1
Anesthesia		
Local	71	-
Epidural	9	1
Spinal	1 (+1)	3
General anesthesia	(2)	52
General and epidural	(1)	17
General and spinal	-	2
Duration of procedure (min)		
Mean (SD)	79 (30.5)*[1]; (109 (59.2))	95.4 (30.9)*[1]
Median (range)	75 (30-165); (90 (60-195))	90 (45-175)
Blood loss (ml)		
Mean (SD)	30.9 (23.8)*[2]; (1000 (823.6))	436.1 (474.5)*[2]
Median (range)	20 (5-150); (850 (300-2000))	300 (10-2500)
Antibiotics		
Antibiotics administered	29 (35.8%); (4 (100.0%))	67 (89.3%)

* For successful procedures; *[1] $p=0.007$, compared to hysterectomy group; *[2] $p<0.001$, compared to hysterectomy group. Characteristics of hysterectomies performed after bilaterally failed embolizations are presented in (parentheses) in the UAE column. LAVH: Laparoscopic-assisted vaginal hysterectomy. LH= Laparoscopic Hysterectomy

a median of 24 months. Other symptoms, besides menorrhagia were prevalent. The majority of women had multiple fibroids. Fibroid volumes were higher in the hysterectomy group.
Logistic regression analysis did not reveal baseline characteristics that could predict randomization outcome, confirming successful randomization.

PROCEDURES

UAE was successfully performed in 72 of 81 patients, of whom five had a unilateral procedure because of single-sided arterial blood flow to the fibroid (procedural success rate: 88.9%). The remaining 11.1% consisted of 5 patients (6.2%) with a unilateral procedure (due to technical failure on the other side) and 4 patients (4.9%) with bilateral unsuccessful UAE. The bilateral impossibility to embolize resulted from bilateral absence of uterine artery flow to the fibroids (n=2), bilateral technical failures (n=1) and extensive anastomoses with the cervix/vagina on one side and a technical failure on the other (n=1). These four patients subsequently underwent hysterectomy, but were analyzed in the UAE group. The total number of arteries that could potentially be embolized in the 88 UAE patients was 152. Of these, 8 arteries were not embolized due to technical inability (technical failure rate: 5.3%).
Table 3 displays the characteristics of both treatments. In most cases (86.1%) target embolization was carried out. For technically successful UAE a median of 1 vial (range: 0.1-3) of PVA was used for each artery.
In the hysterectomy group, all operations were technically successful. Four conversions took place: three procedures (1 LAVH, 1 vaginal and 1 laparoscopic hysterectomy) were converted to a laparotomy. In one abdominal hysterectomy the cervix could not be removed as planned due to adhesions, and a supravaginal hysterectomy was carried out instead. Furthermore, in one vaginal hysterectomy morcellation was necessary for a large fibroid. Most hysterectomies were performed transabdominally (84.0%).
UAE procedures on average took shorter than hysterectomy procedures (79.0 versus 95.4 minutes, p=0.007). Patients subject to UAE had significantly less blood loss than those undergoing hysterectomy (30.9 and 436.1 ml respectively; p<0.001). Total admission time was significantly (p<0.001) shorter in the UAE group (mean: 2.0 days; SD: 2.1; range: 0-13 days) than in the hysterectomy group (mean: 5.1 days; SD: 1.3; range: 2-8 days).

COMPLICATIONS DURING HOSPITAL STAY

Table 4 lists complications occurring during and after the procedures.
Intraprocedural complications were uncommon in both groups. In the UAE group 7 minor complications occurred: 5 post-puncture hematomas, one blood clot in the gluteal artery, which resolved spontaneously, and one case of nausea during the procedure. In the

TABLE 4. Complications until the first scheduled visit (6 weeks after the procedure)

Complication	HOSPITAL STAY		
	UAE*[1] (n=81) n	Hysterectomy (n=75) n	Relative Risk RR (95%CI)
GENERAL			
Nausea	52	42	1.15 (0.89-1.48)
Pain	72	71	0.94 (0.85-1.03)
Febrile morbidity (>38,5ºC)	4	15	0.25 (0.09-0.71)
MINOR COMPLICATIONS			
Vaginal discharge	-	-	-
Pain requiring readmission	-	-	-
Pain/fever requiring readmission	-	-	-
Fibroid expulsion not requiring re-intervention	-	-	-
Hematoma	13	4	3.01 (1.03-8.82)*[1]
Wound abscess	1*[5]	0	
Woundbleeding	1	1	0.93 (0.06-14.54)
Wound dehiscence	0	0	
Urinary tract infection	0	3	.
Urinary retention	0	3	.
Urinary incontinence	-	-	-
Endometritis	0	-	NA
Hot flashes	-	-	-
Anemia requiring transfusion	0	10	.
Hypertension	7*[6]	1	6.48 (0.82-51.45)
Hypotension	0	2	.
Other	1*[7]	2*[8]	0.46 (0.04-5.00)
Total minor complications	23 (in 18 patients)	26 (in 23 patients)	0.72 (0.43-1.23) p=0.23
MAJOR COMPLICATIONS			
Pneumonia	0	0	.
Ileus	0	0	.
Thrombosis	0	0	.
Vesicovaginal fistula	-	-	-
Pulmonary embolism	1	1	0.93 (0.06-14.54)
Intra-abdominal infection	0	0	.
Sepsis	0	0	.
Fibroid expulsion requiring re-intervention	0	0	.
Death	0	0	.
Total major complications	1 (in 1 patient)	1 (in 1 patient)	0.93 (0.06-14.54) p=0.99

hysterectomy group 2 minor complications occurred: one allergic reaction to an anesthetic agent and one small tear in the rectus muscle.

During hospital stay febrile morbidity was significantly less common in the UAE group (4.9%) than after hysterectomy (20.0%; p=0.006; RR: 0.25; 95%CI: 0.09-0.72). Post-intervention fever occurred less frequently in patients who received antibiotics for both the hysterectomy (16.4% versus 50.0%; p=0.046; RR: 0.33; 95%CI: 0.14-0.79) and UAE group (3.4% versus 5.8%; p=0.99; RR: 0.60; 95%CI: 0.07-5.49).

6 WEEKS AFTER DISCHARGE		
UAE*2 (n=81) n	Hysterectomy (n=75) n	Relative Risk RR (95%CI)
25	11	2.10 (1.11-3.97)*3
57	52	1.01 (0.83-1.25)
17	8	1.97 (0.90-4.29)
17	6	2.62 (1.09-6.30)*4
2	-	NA
2	-	NA
12	-	NA
3	2	1.39 (0.24-8.08)
0	1	.
-	-	-
0	1	.
5*12	2	2.31 (0.46-11.57)
1	1	0.93 (0.06-14.54)
6	4	1.39 (0.41-4.73)
2	-	NA
16	15	0.99 (0.53-1.86)
-	-	-
0	1	.
-	-	-
2*9	1*10	-
68 (in 47 patients)	34 (in 30 patients)	1.45 (1.04-2.02) p=0.024
1	0	.
0	0	.
0	0	.
0	1	.
0	0	.
0	0	.
1*13	0	.
1*11	0	.
0	0	
3 (in 3 patients)	1 (in 1 patient)	2.78 (0.30-26.13) p=0.62

NA= not applicable; *1 The UAE group comprises both failed and successful embolizations; *2 Complications of patients with hysterectomies after failed embolizations are described for the 6 weeks after discharge after their hysterectomy procedure; *3 p=0.016; *4 p=0.022; *5 Occurred in a hysterectomy performed after bilaterally failed UAE; *6 Including one patient that was admitted to the medium care unit for extreme hypertension; *7 Spontaneous blood clot in gluteal artery during procedure; *8 Small tear of m. rectus abdominis during surgery, allergic reaction to anesthetic agent during surgery; *9 Gout attack; Liquor spill after epidural anesthesia; *10 Headache after epidural anesthesia; *11 Re-admission, attempt to remove necrotic fibroid hysteroscopically, which only partly succeeded; *12 complication led to a readmission in 3 patients; *13 complication led to readmission in one patient

Hematomas occurred significantly more frequently after UAE, while the hysterectomy group experienced more urinary tract infections and urinary retention. No patients in the UAE group required a blood transfusion compared to 10 patients (13.3%) in the hysterectomy group.
The minor complication rates were 22.2% (95%CI: 13.7-32.8) in the UAE group and 30.7% (95%CI: 20.5-42.4) in the hysterectomy group (RR: 0.72; 95%CI: 0.43-1.23; p=0.23). Major complications were rare and concerned two cases of pulmonary embolisms, one in each group. The major complication rate was 1.2% (95%CI: 0.03-7.2) and 1.3% (95%CI: 0.03-

7.2) for UAE and hysterectomy respectively (RR: 0.93; 95%CI: 0.06-14.54; p=0.99). Both minor and major complication rates did not differ significantly between the two groups.

FOLLOW-UP

Table 5 describes the unscheduled visits within the first six weeks after discharge. In the UAE group 30 patients (37.0% with a total of 46 visits) consulted a physician, mainly for pain and/or fever. In the hysterectomy group 19 patients (25.3% with a total of 24 visits) consulted a physician after discharge for various reasons. This difference was not significant (RR: 1.45; 95%CI: 0.90-2.37, p=0.12).

Readmissions (Table 6) were significantly more common in the UAE group: 9 patients versus 0 patients in the hysterectomy group (p=0.0032). In the UAE group 7 of the 9 (77.8%) readmissions occurred within the first week after discharge from the hospital. Patients were readmitted for pain (22.2%), fever (22.2%) or a combination of both (44.4%). One patient (11.1%) was readmitted for expulsion of a necrotic fibroid. Hysteroscopic removal was attempted, but failed because of cervical dilation which interfered with uterine dilatation. Antibiotics were administered intravenously and the patient stayed in the hospital until fever and pain had subsided. The mean admission time for UAE increased from 2.0 to 2.5 days (SD: 2.7; range: 0-16 days) as a result of readmissions, but remained significantly shorter compared to hysterectomy (p<0.001).

Complications and symptoms between discharge from the hospital and the first routine visit at 6 weeks are shown in Table 4. UAE patients complained of vaginal discharge in 21.0% compared to 8.0% of the hysterectomy patients (p=0.022). 14.8% of UAE patients experienced vaginal loss of fibroid tissue. Hot flashes were present in 19.8% (UAE) and 20.0% (hysterectomy) of patients. 4 cases of pain and/or fever that required readmission were classified as minor complications, since the definition of major complications which we used (as described in the methods section) did not apply here.

Three patients (3.7%) in the UAE group had major complications: pneumonia in a patient with a history of recurrent pneumonia due to asthmatic disease (n=1); re-intervention because of an incomplete fibroid expulsion (n=1) and septicemia (n=1). One patient (1.3%) in the hysterectomy group was diagnosed with a vesicovaginal fistula, which was surgically repaired beyond the 6 weeks follow-up period (not reported in Table 6).

The minor complication rate in the first 6 weeks after discharge was significantly higher in the UAE group than in the hysterectomy group: 58.0% (95%CI: 46.5-68.9) and 40.0% (95%CI: 28.9-52.0) respectively (RR: 1.45; 95%CI: 1.04-2.02; p=0.024). The major complication rate in the first 6 weeks after discharge was 3.7% (95%CI: 0.8-10.4) and 1.3% (95%CI:

TABLE 5. Unscheduled visits after discharge until first routine visit (6 weeks after procedure)

Contact	Symptom(s)	UAE n=81 Number of contacts	Hysterectomy n=75 Number of contacts
General Physician	Pain	3	3
	Fever	5	0
	Vaginal bleeding	0	3
	Groin haematoma	1	0
	Constipation	0	2
	Blood pressure issues	1	2
	Other	3*[1]	4*[2]
	Total	13 (in 10 patients)	14 (in 12 patients)
Gynecologist	Fever	4	0
	Fever & pain	7	0
	Fever & vaginal bleeding	0	1
	Pain	12	2
	Pain & vaginal discharge	2	1
	Pain & vaginal bleeding	3	0
	Vaginal bleeding	0	3
	Vaginal discharge	2	0
	Wound dehiscence	0	2*[3]
	Other	0	1*[4]
	Total	30 (in 22 patients)	10 (in 8 patients)
Lung specialist	Fever, dyspnoe: pneumonia	3	0
	Total	3 (in 1 patient)	0
	Total number of visits	45	24
	Total number of patients	30*[5]	19

*[1] checking hemoglobin level; gout attack; sensitive breast; *[2] coughing, dizzy and constipation; stomach pain; urge incontinence complaints; vaginal itch; *[3] same patient; *[4] severe hair loss; *[5] RR: 1.45 (95%CI: 0.90-2.37; p=0.12) compared to number of patients in the hysterectomy group

0.03-7.2) for UAE and hysterectomy respectively (RR: 2.78; 95%CI: 0.30-26.13; p=0.62) and did not differ significantly.

The overall minor complication rate (i.e. from the procedure until the six week routine visit) was 64.2% (95%CI: 52.8-74.6) (52 patients) in the UAE group compared to 56.0% (95%CI: 44.1- 67.4) (42 patients) in the hysterectomy group (RR: 1.12; 95%CI: 0.87-1.46; p=0.38). The overall major complication rate was 4.9% (95%CI: 1.4-12.2) (4 patients) in the UAE group compared to 2.7% (95%CI: 0.3-9.3) (2 patients) in the hysterectomy group (RR: 1.85; 95%CI: 0.35-9.82; p=0.68). Both findings were not statistically significant. Also when only abdominal hysterectomies were compared with UAE, overall major and minor complication rates did not differ significantly (p=0.28 and p=0.70). The difference in hospitalization time remained statistically significant (p<0.001). Radiologists' experience with UAE was not

TABLE 6. Readmissions after UAE until first routine visit (6 weeks after the procedure)

Reason for readmission	n	Course	Days after discharge	Length of stay
Fever	1	Antibiotics administered, urine and cervix cultures positive for Streptococcus	4	3
	1	Antibiotics administered for urinary tract infection	4	4
Fever and pain	1	Analgesics and antibiotics administered for urinary tract infection	3	5
	2	Analgesics and antibiotics administered, no definite diagnosis	3	2
			3	4
Pain	2	Analgesics administered	1	1
			4	1
Septicaemia	1	MRI scan revealed an infectious process cranial in the uterus, which drained itself vaginally. Antibiotics and analgesics administered	51	11
Myoma nascens	1	Failed attempt to hysteroscopically remove necrotic tissue due to cervix dilation. Antibiotics and analgesics administered.	23	6

No hysterectomy patients were readmitted to the hospital

associated with the technical failure rate. Less experienced hospitals were not associated with higher complication or readmission rates.

DISCUSSION

Current knowledge on UAE derives from numerous uncontrolled case series and only one small pre-consent randomized trial of moderate quality [17]. According to the National Institute of Clinical Excellence (NICE), the limitations of the available literature only allow tentative conclusions about the safety and efficacy of UAE [18], especially since highly selected patient inclusion and high loss to follow-up bias the results. NICE strongly recommends the initiation of randomized controlled trials, which is exactly what we did here.

We deliberately chose to compare UAE with hysterectomy, not with myomectomy [19], for several reasons. Firstly, hysterectomy is the standard procedure of choice to eliminate all fibroid related complaints. In our view, myomectomy should be preserved for those women with symptomatic uterine fibroids with a strong desire for future pregnancy. Since UAE is considered to be contra-indicated for women desiring pregnancy, a randomized comparison with myomectomy might even be considered unethical at this stage [20]. In the absence of randomized data, we judged it more ethical to perform a study at the other end of the clinical spectrum, i.e. in women facing hysterectomy as the last resort for their fibroid related complaints. Although hysterectomy is an absolute cure for menorrhagia, possible sequalae,

e.g. incontinence, vaginal vault prolapse, risk for premature ovarian failure, long recovery, high costs and the desire of some patients to preserve their uterus, justify serious consideration of alternative therapies such as UAE.

The procedural success rate (88.9%) was comparable to the results of the aforementioned small semi-randomized trial, but lower than the success rates reported in most other studies, thereby illustrating the necessity of randomized data collection [17].

The technical failure rate (5.3%) was higher than the 0.5%- 2.5% reported in large case series [2;3;5;21], but similar to the technical failure rate of 5.0% reported in the only semi-randomized trial [17], due to several possible reasons. Firstly, our study is a mix of both academic and non-teaching hospitals whereas UAE in the reported case series was mostly performed in highly specialized single-centers, decreasing the generalizability of those results [22]. However, in our study experience of the interventional radiologist was not associated with outcome. Moreover, one series performed a second embolization attempt after initial technical failure, which obviously improves technical success rates [4]. Generally, results from randomized controlled trials can substantially differ from those in case series because of publication bias and patient selection criteria [23;24].

Mean hospital stay was significantly shorter for UAE than for hysterectomy. Mean hospital stay for UAE was longer than in some studies, but in our experience most patients need more care [25;26]. Therefore we would not recommend performing UAE as an outpatient procedure. Surprisingly, the number of unscheduled visits was higher in the UAE group. Readmission rates after UAE within the first 6 weeks (11.1%) were higher compared to other reports (2.9%-5.0%), although the reasons for readmission were similar [17;27]. The experimental status of the UAE procedure could be the reason why physicians were more inclined to see patients and readmit them more quickly. Most readmissions in our study occurred within the first week after discharge (77.8%), underlining the need for adequate follow up during this period. None of our hysterectomy patients were readmitted within the first 6 weeks, while Pinto et al. found a readmission rate of 5.0% after hysterectomy [17]. Since most hysterectomy patients were still in the hospital when most readmissions in the UAE group occurred, the comparison is not completely fair: if UAE patients would stay in the hospital as long as hysterectomy patients only 2 readmissions would have occurred.

Overall major and minor complication rates in both groups were comparable, but minor complications in the period between discharge and the first 6 weeks' visit were significantly higher in the UAE group. Our study therefore cannot support the suggestion made by others [28] that UAE has a lower complication rate than hysterectomy, again stressing the need for randomized studies. A detailed comparison of complication rates with other studies is hampered by the fact that various studies apply different classification systems for reporting

complications. Major complications were rare in our study. Although many series reported emergency hysterectomy rates up to 1.3% within the first weeks after UAE, no such procedures occurred in our patients [3;4;21;27].

There are several limitations to our study. Firstly, 21 (11.9%) patients withdrew from the study after randomization before treatment. Their baseline characteristics, however, did not differ from those being treated. Secondly, given the low major complication rates, our study size was too small to detect any difference in major complication rates, and definite conclusions therefore cannot be drawn. In contrast we did find differences in minor complication rates and length of hospital stay, so lack of power was not an issue here. We used no objective criteria for menorrhagia but relied on subjective appreciations of our patients. By doing so, the generalizability of our findings is probably enhanced: included patients represent those seen in daily practice where the decision to perform a hysterectomy is not based on objective measurements (e.g. pictorial charts) either.

In summary, we could not find any differences in major complication rates between UAE and hysterectomy. Unsuccessful UAE procedures, however, seem to occur more often than previously reported. Hospital stay is significantly shorter for UAE. The higher minor complication rate after discharge in the UAE group, as well as the re-admission rates and unscheduled visits emphasize the necessity for careful follow up and clear instructions to the patient. Although the study results are supportive for UAE, the question as to whether UAE is a good alternative for hysterectomy depends on the balance of efficacy, costs, and quality of life, and still remains to be answered.

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3

UTERINE ARTERY EMBOLIZATION IN THE TREATMENT OF SYMPTOMATIC UTERINE FIBROIDS (EMMY TRIAL): PERIPROCEDURAL RESULTS AND COMPLICATIONS

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ABSTRACT

Purpose

Uterine artery embolization (UAE) is an emerging treatment for symptomatic uterine fibroids. This study was performed to evaluate the peri-procedural results of the UAE procedure and to identify risk factors for technical failure, post-intervention fever, other complications and pain.

Methods

As part of a multi-centre, randomized trial, comparing UAE with hysterectomy in patients with symptomatic uterine fibroids, 81 patients underwent UAE. Univariate and multiple analyses were used to identify predictors for technical failure, post-intervention fever, complications as defined by the Society of Interventional Radiology (SIR) and pain scores.

Results

The technical failure rate according to SIR guidelines was 5.3% (95%CI: 2.3-10.1). The procedural failure rate was 17.3% (95%CI: 9.8-27.3). Bilateral failure occurred in 4/81, unilateral in 10/81 patients. Technical failure was mainly due to difficult anatomy (3.7%) or absence of the uterine artery (3.1%). The overall complication rate was 28.4% during hospital stay and 60.5% after discharge until 6 weeks. The risk of technical failure was found to increase with a single fibroid (OR: 6.21; 95%CI: 1.65-23.41; p=0.007) and/or a small uterine volume (<500cc) (OR: 10.8; 95%CI: 1.25-93.36; p=0.03). The amount of embolization material was associated with the onset of post-intervention fever (OR: 2.05; 95%CI: 1.09-3.87; p=0.027), major complications (OR: 5.68; 95%CI: 2.05-15.75; p=0.001) and high pain scores (OR: 1.97; 95%CI: 1.08-3.58; p=0.027).

Conclusion

The procedural failure rate for UAE was higher than reported by others, mainly due to difficult anatomy and absence of a uterine artery. The risk of procedural failure was increased for patients with single fibroids and small uterine volumes. A clear dose-effect response was revealed between the amount of embolization material used and the risk for post-intervention fever, major complications, and severe pain.

INTRODUCTION

Uterine artery embolization (UAE) has become increasingly popular for the treatment of uterine fibroids since its introduction in 1995 [1]. Present knowledge on UAE derives from several large uncontrolled case series [2-6]. Technical failure and complications rates are reported to be low in the available literature. Until now, only limited information has been available about possible risk factors for technical failure and complications. This report is part of a multicentre, randomized-controlled trial comparing uterine artery EMbolization with hysterectoMY (EMMY-trial) in the treatment of symptomatic uterine fibroids causing menorrhagia. In this article we analyze the technical results of the UAE procedures, describe anatomic variations and identify risk factors for technical and procedural failures, occurrence of vasospasm, onset of post-intervention fever, occurrence of complications and high post-procedural pain scores.

METHODS

STUDY DESIGN

The data presented herein were gathered as part of the ongoing randomized controlled EMMY trial which compares UAE with hysterectomy, and is conducted in 34 Dutch hospitals.

Patients were included when: 1) the clinical diagnosis of uterine fibroids had been confirmed by ultrasonography, 2) menorrhagia was the predominant complaint among other probably fibroid related signs and symptoms (i.e. patients who exclusively had bulk-related symptoms and/or pain but no menorrhagia, were not included), 3) hysterectomy was thought to be the ultimate solution and other treatment options were unsuitable or had failed to provide symptomatic relief, 4) they were premenopausal, 4) preservation of the uterus was not warranted for future pregnancy, 5) the following disorders were absent: renal failure (creatinine >150 mmol/L), active pelvic infection, clotting disorders, allergy to contrast fluid, (suspected) uterine malignancy, submucosal fibroids protruding by >50% within the uterine cavity or pedunculated abdominal fibroids.

Randomization was performed 1:1 to UAE or hysterectomy, using a computer-based minimisation scheme ('balancing procedure'), stratified for study centre. Written informed consent was obtained in all patients. The study was approved by the Dutch Central Committee Involving Human Subjects (www.ccmo.nl) and by local ethic committees. This article specifically focuses on those patients allocated to UAE.

PRE-PROCEDURAL EVALUATION

All patients were referred to the gynecology outpatient clinic, and after assessment of the inclusion- and exclusion criteria, eligible patients were included by the gynecologist. The majority of women were seen by the radiologist for the first time shortly before the procedure.

Before undergoing UAE, all patients underwent a clinical evaluation, including a pelvic ultrasound and magnetic resonance imaging (MRI). MR imaging was performed using a standardized imaging protocol, but using different brands of 1.0 and 1.5 T MRI scanners all equipped with a phased array body coil. For both ultrasound and MRI, the largest fibroid was indicated as the dominant fibroid. With ultrasound the following parameters were measured. The uterus and the dominant fibroid were measured in three dimensions, i.e. longitudinal (D1), anterior-posterior (D2), and transverse (D3). Volumes were calculated using the formula [D1 $\times$ D2 $\times$ D3 $\times$ 0.5233] [7]. The location of the dominant fibroid was defined as being intramural, submucosal (the epicenter of the fibroid is closer to the uterine cavity than to the myometrium), subserosal (the epicenter of the fibroid is closer to the abdominal cavity than to the myometrium) or inconclusive [8]. The total number of fibroids was recorded. The flow in the dominant fibroid was measured using color-doppler and graded hypovascular, normovascular or hypervascular compared to the myometrium. The signal intensity of the dominant fibroid on MR-imaging was classified as hypointens, isointens, hyperintens or mixed compared to normal myometrial tissue. Blood work was carried out before, and 1 day and 6 weeks after UAE, and included hemoglobin levels, leucocytes and creatine kinase.

UAE-PROCEDURE

Patients were advised to discontinue any GnRH analogues at least 1 month before the UAE [9;10]. Note was made whether a patient was menstruating during the procedure. Patients were admitted to the gynecology department for peri-procedural care, since Dutch radiologists have no clinical ward of their own to admit patients. UAE was performed on the intervention radiology department as a sterile procedure under local or epidural anesthesia. All radiologists were experienced in interventional radiology, including embolization techniques in general. However, UAE was not for all radiologists a routine procedure. The first 2-3 procedures in each hospital were supervised by an interventional radiologist (JR), with ample experience in UAE (>50 UAE procedures).

Patients received an intravenous line and a Foley catheter prior to UAE. The use of prophylactic antibiotics was not standardized. Femoral artery access could be either unilateral or bilateral. A 4- or 5-French catheter was introduced into the femoral artery and advanced over the aortic bifurcation to the contralateral internal iliac artery, and digital subtraction angiography

was performed to identify the origin of the uterine artery. The size of the uterine artery was classified as small, normal or wide. In case of spasm the policy was to wait, but a microcatheter and/or spasmolytics could be used within the study protocol. Polyvinyl alcohol particles (PVA, Contour, Boston Scientific, Beek, The Netherlands) with a size of 355-500 μm were used in all procedures. One vial contains 1cc dry volume of PVA. Only if an anastomosis with the ovarian artery was observed, 500-700 μm particles were used [11]. PVA, mixed with contrast fluid and saline, was injected into each uterine artery until parenchyma filling of the fibroids had stopped (i.e. target embolization) or until the main uterine artery was blocked and stasis of contrast occurred (i.e. selective embolization).

According to the Society of Interventional Radiology guidelines, UAE was considered successful whenever bilateral UAE was established; unilateral UAE was only considered a successful procedure if single-sided uterine arterial flow to the fibroids was present [12]. If a uterine artery was absent and flow to the fibroids came solely from the ovarian artery, the procedure was stopped, because of a presumed high risk for ovarian damage, and was considered a procedural failure. Also in case of extensive collaterals to the cervix and vaginal wall, the procedure was stopped and considered a procedural failure. Both the procedural failure rate (including all failures) and the technical failure rate (all failures, excluding the ones due to absent arteries, or arteries with no flow or arteries with extensive collaterals, necessitating discontinuation of the procedure) were calculated. No second attempt was performed in unsuccessful cases. After the embolization all catheters were removed and groin pressure was applied at the puncture site for 10-15 minutes. Arterial closure devices were not used routinely.

All peri-procedural characteristics were recorded. Anatomical variations of the uterine artery as identified by the interventional radiologist were categorized as follows: type I (the uterine artery arises from the inferior gluteal artery), type II (the uterine artery is the second or third branch of the inferior gluteal artery, type III (the inferior gluteal, superior gluteal and the uterine artery all arise at the same level), type IV (the uterine artery arises proximal to the origin of the inferior gluteal and superior gluteal arteries) [13] or inconclusive/absent.

After the procedure women stayed at the gynaecology ward for further care. We advised the use of the following peri-procedural pain protocol to all participating units: to start with paracetamol (3 x 1000 mg) and NSAID's (diclofenac 3 x 50 mg) before, during and after the procedure and to give opiates (morphine 10 mg, max. of 6 times a day) whenever pain control was insufficient. If pain was still insufficiently controlled by these measures, epidural anesthesia was suggested. The level of pain was scored using the Numerical Rating Scale (NRS) [14] and recorded at 1-3-6-12-24-48 hours after the UAE as long as the patient was still admitted. An average pain score exceeding 5 (0-10 scale) was considered high. All

patients were advised to stay in hospital for at least one night. At hospital discharge, patients received instruction to contact their gynecologist whenever uncontrollable pain, persistent fever or expulsion of fibroids occurred. One week after UAE, a telephonic inquiry was carried out by the gynecologist in all patients. At 6 weeks all patients were seen routinely at the gynecology outpatient clinic. All complications (i.e. procedural and post-procedural) were prospectively recorded until 6 weeks after UAE and were retrospectively classified using the SIR classification (which were issued after the start of our study) (Table 1) [15].

TABLE 1. Complications classified according to SIR*[1]

SIR class	Description
A	No therapy, no consequences
B	Nominal therapy, observation, no consequences
C	Required therapy, minor hospitalization (< 48 h)
D	Major therapy, unplanned increase in level of care, prolonged hospitalization (> 48 h)
E	Permanent adverse sequelae
F	Death

*[1] SIR: Society of Interventional Radiology

STATISTICAL ANALYSIS

Data entry was performed using SPSS data entry for Windows 3.0. All data entries were visually double checked by an independent second investigator. Analysis was done using SPSS statistical software (version 11.5.1).

We investigated the effect of experience of the radiologist and hospitals (experienced defined as having performed > 10 UAE procedures) in performing UAE on technical failures, complications and readmissions using χ^2-tests or Fisher Exact tests if appropriate. 95% Confidence intervals were calculated for each complication.

Logistic regression analysis was performed to investigate candidate variables for being associated with the following outcomes: 1) failed procedures (i.e. both procedural and technical failures), 2) spasm during the procedure, 3) fever (>38.5°C/101.3°F), 4) minor or major complications and 5) high NRS-pain scores. First, univariate logistic regression analysis was performed with the following baseline characteristics for all outcome measures: age, etnicity, parity, BMI, smoking status, co-morbidity, uterus volume (<500/≥500cc), volume (<100/≥100cc) and location (submucosal, intramural, subserosal and inconclusive) of the dominant fibroid, total number of fibroids (1/>1) and total number of PVA vials used. For the analysis on procedural failures, additional variables analyzed were: duration of menstrual symptoms, previous treatment, color doppler-flow characteristics of the dominant fibroid, T_2-signal intensity of the dominant fibroid, prior use of GnRH analogues, anatomical variation and diameter of the uterine artery. For the occurrence of vasospasm, additional variables

analyzed were: prior use of GnRH analogues, anatomical variation and diameter of the uterine artery. For the onset of post-intervention fever, complications or high pain scores, these were pre-procedural anemia, diabetes, menstruation during UAE, use of antibiotic prophylaxis, total procedure time [defined as the time from the first femoral puncture until the moment when groin pressure was applied and the patient was ready to leave the intervention room] (<75 versus >75 min), level of creatine kinase 1 day after UAE (<170 versus >170 U/l).

Covariates with a univariate p value ≤0.10 were subsequently entered in the multiple logistic regression analysis. Odds ratios and 95% confidence intervals (95%CIs) of statistically significant independent determinants were reported. The Goodman and Kruskal gamma test was used to investigate the association between the uterine volume or the dominant fibroid volume and the diameter of the uterine artery. P-values <0.05 were considered statistically significant.

RESULTS

PATIENTS

Between March 2002 and February 2004, a total of 88 women were randomly allocated UAE, 81 of whom (92.0%) underwent the assigned procedure. Patients' baseline characteristics are listed in Table 2. Of the seven dropouts, 6 patients withdrew from the trial; one woman preferred to try alternative medicine while 5 women preferred a hysterectomy on second thought and one patient was excluded, because the MRI scan prior to the UAE showed no fibroids in contrast to earlier ultrasound findings.

PROCEDURES

In 14 of the 81 patients (17.3%; 95%CI: 2.3-10.1) UAE failed on one or both sides. Bilateral failure of the procedure occurred in 4 patients (4.9%) who subsequently underwent a hysterectomy. Ten patients had a unilateral UAE (12.3%) [16].

The most common reason for procedural failures was difficult anatomy (n=6 arteries; 3.7%). The uterine artery was either extremely small or tortuous, or the origin of the vessel was too steep or tortuous to allow access. Another important reason for UAE failure was the absence of the uterine artery (n=5 arteries; 3.1%). In three patients a large ovarian artery was noted to be the dominant source of uterine vascularity. Other reasons were the absence of any parenchyma blush or visible flow to the fibroid (n=4 arteries) (2.5%). Spasm during the procedure, obstructing free flow of embolization material, occurred in 2 arteries (1.2%). In

TABLE 2. Baseline characteristics

	n=81 n (%)
Age (years)	
< 35-40	14 (17.3)
40-45	28 (34.6)
> 45	39 (48.1)
Mean (SD)	44.8 (4.7)
Body Mass Index (weight (kg) / length $(m)^2$)	
0-25	50 (61.7)
> 25	31 (38.3)
Mean (SD)	26.9 (5.5)
Parity	
0	28 (34.6)
≥ 1	53 (65.4)
Ethnicity	
Black	21 (25.9)
White	50 (61.7)
Other	10 (12.3)
Smoking status	
Current smoker	19 (23.5)
Non-smoker	62 (76.5)
Number of fibroids	
1	34 (42.0)
>1	47 (58.0)
Median (range)	2 (1-20)
Uterine volume (cm^3)	
<500	56 (69.1)
>500	25 (30.9)
Median (range)	457.8 (1.2-673.5)
Dominant fibroid volume (cm^3)	
<100	52 (64.2)
>100	29 (35.8)
Median (range)	119.9 (31.4-3004.8)
Dominant fibroid location	
Submucosal	16 (19.8)
Intramural	47 (58.0)
Subserosal	9 (11.1)
Inconclusive	9 (11.1)
Prior surgical treatment	
Hysteroscopic myomectomy	5 (6.2)
Laparoscopic myomectomy	0 (0.0)
Laparotomic myomectomy	6 (7.4)
Hysteroscopic endometrium resection	3 (3.7)
Curretage	1 (1.2)

Values in parentheses are percentages unless otherwise specified

one patient, embolization was not performed because the risk of non-target embolization was judged as being unacceptably high, because of extensive collaterals to the vagina and cervix that could not be bypassed (0.6%).

Consequently, the total number of arteries that could potentially be embolized in 81 patients was not 162, but 152 (10 uterine arteries were not embolizable); thus the true technical failure rate, therefore, is 8/152=5.3% (95%CI: 2.3-10.1). Prior experience of the radiologists in performing UAE's was not associated with the technical failure rate (p=0.43) nor the procedural failure rate (p=0.38).

Five patients stopped using GnRH analogues before the procedure with an interval ranging from 14-60 days. Of these 5 patients 3 were failures, one patient had a unilateral failure due to a difficult anatomy, one patient had a unilateral failure because no detectable flow to the fibroid was present, while another patient had a bilateral failure, due to undetectable flow to the fibroid.

Eighteen patients (22.2%) underwent UAE during a menstrual period. Prior to the UAE (80/81) 99% of patients received a Foley catheter and a minority (29/81; 35.8%) were given antibiotic prophylaxis. For pain relief patients received local, epidural or spinal anesthesia in respectively 87.7%, 11.1% and 1.2% of cases. Bilateral access to the femoral artery was used in most patients (95.1%). In most cases (86.1%) target embolization was carried out. For technically successful procedures the quantity of embolic agent ranged from 0.5-5 vials PVA per procedure (median: 2 vials, mean: 1.85 vials). PVA particles sized 355-500 μm were used in 63 (81.8%) patients. Particles with a size of 500-700 μm or a combination of 355-500 μm and 500-700 μm were used in 5 (6.5%) and 8 (10.4%) patients showing uni- or bilateral uterine-ovarian anatomosis respectively.

The majority of UAE procedures were performed with a variety of 4- and 5-French catheters in 70.4% and 29.4%, respectively. In 26 procedures (32.1%) a total of 32 microcatheters were used. Microcatheters were used mainly because of a difficult anatomy, e.g. a small and tortuous origin of the uterine artery (n=19; left: 14, right: 5). Other reasons were to bypass cervical and vaginal arterial branches (n=4; left: 2 right: 2) or spasm (n=5; left: 3, right: 2) or because of slow flow in the uterine artery (n=2; left: 1, right: 1) or because microcatheters were used routinely (n=2; left:1, right:1).

Spasm occurred in 18 vessels during the procedure. In 13 cases waiting solved the problem, while in 5 cases microcatheters were used and in 1 case the procedure was discontinued because of continuing spasm despite these measures. One patient with a successful procedure on one side but severe spasm in the contralateral uterine artery was treated with two coils instead of PVA, because of the substantial risk of backflow. Although flow in both

uterine arteries ceased, the procedure was considered a unilateral failure. Vasodilators were not used in any of the procedures.

Only in one very obese patient an angioseal (St. Jude Medical, St. Paul, MN) was used to close both femoral puncture sites. The procedure time averaged 79 minutes (SD: 30.5). The average procedure time for bilaterally successful cases was 75 minutes (SD: 27.3) and for unsuccessful cases 96 minutes (SD: 39.5; for the difference p= 0.075). The radiation dose averaged 377.7 Gycm^2. The amount of blood loss was minimal in all patients (mean: 30.9 cc, range: 5-150). Total admission time was on average 2.0 days (SD: 2.1; range: 0-13 days).

ANATOMY

Anatomical variations were classified as follows: Type I, 29.0%, Type II, 6.8%, Type III, 35.2%, Type IV 14.8% (Table 3). In 3.1% of cases no uterine artery was present and in 11.1% the classification of the uterine artery was unknown or inconclusive. Of all patients 43.2% showed symmetrical anatomical variations, while 40.7% showed asymmetrical anatomical variations. In 16.1% of patients the symmetry could not be established. Uterine-ovarian

TABLE 3. Uterine artery anatomy

Anatomical variation	n=162 potential arteries n (%)
Type I	47 (29.0)
Type II	11 (6.8)
Type III	57 (35.2)
Type IV	24 (14.8)
Absent artery	5 (3.1)
Unknown/inconclusive	18 (11.1)
Uterine-ovarian artery anastomosis *1	15 (9.3)
Uterine-uterine artery anastomosis	1 (0.6)

*1 left side: 5, right side: 10, missing: 4

anastomosis were present in five cases on the left side (3.1%) and in ten (6.2%) on the right side. One patient (0.6%) showed a direct transversal anastomosis between both uterine arteries, which became apparent only after the embolization of the right side was finished and contrast fluid was administered on the contralateral side. This was an incidental finding. The case was classified as a successful procedure since both arteries were embolized with disappearance of parenchyma blush and residual flow in both uterine arteries.

TABLE 4. Complications during hospital stay

Complication	n	SIR *1 Class A	SIR Class B	SIR Class C	SIR Class D	SIR Class E	SIR Class F
Hematoma	12	12	-	-	-	-	-
Hypertension	7	3	4	-	-	-	-
Pulmonary embolism	1	-	-	-	1	-	-
Spontaneous clot in gluteal artery	1	1	-	-	-	-	-
Prolonged stay in hospital due to pain	7	-	4	3	-	-	-
Total number of complications*2	28	16	8	3	1	0	0
Total number of patients(%,95%CI)	23	15	8	3	1	0	0
	(28.40%, 18.9-39.5)	(18.52%, 10.7-28.7)	(9.88%, 4.4-18.5)	(3.70%, 0.8-10.4)	(1.23%, 0.03-6.7)	0%	0%

*1 SIR: Society of Interventional Radiology; *2 28 complications in 23 patients, 4 patients with 2 complications (1 patient with complications in the same SIR class), 1 patient with 3 complications in different SIR classes

COMPLICATIONS

Table 4 summarizes all complications during hospital stay. The minor complication rate and major complication rate during hospital stay were 25.9% (95%CI: 16.8-36.9) and 4.9% (95%CI: 1.36-12.2) respectively. Six (7.4%) intraprocedural complications occurred: 5 post-puncture hematomas and in one patient an intraluminal filling defect (i.e. thrombus) in the gluteal artery was seen during a control angiography of the left uterine artery, which at a later stage had resolved spontaneously. The patient was not treated with anti-coagulants. No vascular perforations occurred.

A total of 23 (28.4%) patients experienced 28 complications during hospital stay (Table 4). The majority of SIR-defined complications were minor: class A: 18.5% and class B: 9.9%. The most frequent minor complication was groin hematoma (14.8%). A total of 7 patients (8.6%) suffered sudden hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) after UAE. Of the 7 patients, 2 had pre-existent hypertension and were stable with anti-hypertensive medication, while the other 5 had no previous history. In all patients the rise in blood pressure was observed immediately after the UAE procedure, except for one patient in whom the hypertension started two days after the procedure. This woman experienced 4 days after UAE a pulmonary embolism. In three patients the internist was consulted and medication was started, while three patients only had a temporarily increase in blood pressure and were treated expectantly. Four patients (4.9%) had a major complication during hospital stay. Three women required a prolonged stay exceeding 24 hours because of severe pain and one woman was diagnosed with pulmonary embolism after a unilateral UAE procedure due to an absent right uterine artery. Furthermore the

TABLE 5. Complications from discharge until 6 weeks, including unscheduled visits and re-admissions

Complication	n	SIR*[1] Class A	SIR Class B	SIR Class C	SIR Class D	SIR Class E	SIR Class F
Hematoma	4	4	-	-	-	-	-
Rash	1	1	-	-	-	-	-
Gout attack	1	-	1	-	-	-	-
Post lumbar puncture headache after epidural anesthesia	1	-	1	-	-	-	-
Fibroid expulsion no intervention	11	11	-	-	-	-	-
Fibroid expulsion/ with intervention	1	-	-	-	1	-	-
Vaginal discharge	20	19	1	-	-	-	-
Prolonged pain	16	7	7	2	-	-	-
Prolonged pain + fever	2	-	-	-	2	-	-
Subfebrile fever + menorraghia	1	1	-	-	-	-	-
Endometritis	2	-	1	1	-	-	-
Pneumonia	1	-	1	-	-	-	-
Sepsis	1	-	-	-	1	-	-
Urinary tract infection	5	-	3	-	2	-	-
Urinary incontinence	6	6	-	-	-	-	-
Urinary retention	1	1	-	-	-	-	-
Hot flashes	16	16	-	-	-	-	-
Total number of complications*[2]	90	66	15	3	6	0	0
Total number of patients (%, 95%CI)	51 (62.96%, 51.5-73.4)	42 (51.85%, 40.5-63.1)	15 18.52%, 10.7-28.7)	3 (3.70%, 0.78-10.4)	6 (7.41%, 2.76-15.4)	0 0%	0 0%

*[1] SIR: Society of Interventional Radiology; *[2] 90 complications in 51 patients; 15 patients with 2 complications (7 times in the same SIR class), 9 patients with 3 complications (12 times in the same SIR class), 2 patient with 4 complications (5 times in the same SIR class)

procedure was uneventful. Two days later she developed a high blood pressure, which was treated with anti-hypertensive medication and two days following this event she developed chest pain. No cardiac origin was found, but the ventilation perfusion scan showed signs of pulmonary embolism. The patient received anti-coagulant therapy and recovered without any further problems.

Table 5 lists complications occurring between discharge and the first planned routine visit, and also include unscheduled visits and re-admissions. The rates of minor and major complication between discharge and 6 weeks were 53.1% (95%CI: 41.7-64.3) and 11.1% (95%CI: 5.2-20.1) respectively. A total of 90 complications occurred in 51 (63.0%) patients. The majority was minor complications (SIR class A: 51.9% and class B: 17.3%). The most frequent minor complications were vaginal discharge, hot flashes and prolonged pain. One patient, a 47-year old woman who had received epidural anesthesia followed by a bilateral successful UAE procedure, presented two days after discharge with orthostatic headache and tinnitus. The puncture opening was clean. No indication for meningitis was found and

the diagnosis post-lumbar puncture headache due to liquor leakage was made. Treatment consisted of 72 hours bed rest, sufficient fluid intake, 3 times a day 1000 mg of caffeine and avoidance of pressure increasing movements. Symptoms subsided and further clinical follow-up was uneventful.

There were 46 (37.0%) unscheduled visits to a physician by 30 patients within the first six weeks after discharge, mainly because of pain and/or fever. Nine patients (11.1%) experienced a SIR–defined major complication after discharge. All were readmitted to hospital, 7 of whom (77.8%) within the first week after discharge. Class C complications occurred in 3 patients (3.7%): one case of endometritis which was treated successfully with antibiotics, while two others were hospitalized for prolonged severe pain. Of the six complications coded as D, two patients had urinary tract infections and were treated with antibiotics; two were readmitted for prolonged pain in combination with fever without obvious focus, and successfully treated with antibiotics. One patient developed septicemia and presented with fever in combination with a foul-smelling vaginal discharge. The patient recovered readily on antibiotic treatment without further sequelae or interventions. One patient was seen ten days after an uneventful bilateral UAE procedure complaining of pelvic pain and vaginal discharge. No fever was noted. On ultrasonographic examination a fibroid was seen in the uterine cavity. Analgesics were prescribed and the patient was treated expectantly. Thirteen days later she returned to hospital and during physical examination a fibroid was partly protruding from the cervix. Hysteroscopic removal was attempted, which succeeded only partly because cervical dilation interfered with the procedure. The clinical follow-up of the patient was uneventful. Pathological examination confirmed the diagnosis of a necrotic fibroid. All other 11 fibroid expulsions were reported by patients at 6 weeks follow-up, but no clinical observation or pathological examination could indeed confirm this.

No emergency hysterectomies were performed and no class E and F complications occurred. The mean admission time for UAE increased from 2.0 to 2.5 days (SD: 2.7; range: 0-16 days) when readmissions were added. Less experienced radiologists and hospitals were not associated with higher complication or readmission rates.

RISK FACTORS

Table 6 lists the risk factors associated with failed procedures, the occurrence of post-intervention fever, complications and high pain scores.

Unilateral or bilateral failure occurred in 14 of the 81 patients. The risk of failure was associated with a single fibroid in the univariate analysis (OR: 4.48; 95%CI: 1.27-15.83), as well as the multiple analysis (OR: 6.21; 95%CI: 1.65-23.41). A relatively small uterine volume (<500 cc) was also associated with a higher risk of failure (OR: 10.8; 95%CI: 1.25-

TABLE 6. Univariate and multiple analysis of riskfactors associated with procedural failures, fever (≥38.5°C), major complications (SIR class C, D, E and F)*[1] and high (>5) pain scores*[2]

	Odds Ratio	95%CI*[3]	p-value
PROCEDURAL FAILURES n=14			
Univariate analysis			
Single fibroid	4.48	1.27-15.83	0.02
Volume uterus (<500 cc)	7.26	0.89-58.92	0.064
Age 0-40 yrs	2.15	0.56-8.23	0.064
40-45 yrs	0.14	0.02-1.22	0.064
>45 yrs	1		
Multiple analysis			
Single fibroid	6.21	1.65-23.41	0.007
Volume uterus (<500 cc)	10.8	1.25-93.36	0.03
POST-INTERVENTION FEVER (>38.5°C/101.3 °F) n=19			
Univariate analysis			
Each additional vial of PVA	2.17	1.15-4.11	0.017
Procedural time (< 75 min)	3.86	1.01-14.69	0.048
Volume uterus (≥ 500 cc)	2.59	0.89-7.51	0.08
Volume dominant fibroid (≥100 cc)	2.52	0.88-7.19	0.085
Multiple analysis			
Each additional vial of PVA	2.05	1.09-3.87	0.027
MAJOR COMPLICATION (≥ 1) n=12			
Univariate analysis			
Each additional vial of PVA	5.68	2.05-15.75	0.001
Volume dominant fibroid (≥100 cc)	4.57	1.24-16.86	0.022
Volume uterus (≥ 500 cc)	3.97	1.12-14.09	0.033
Creatine kinase (>170 U/l)	3.77	1.01-14.05	0.048
Multiple analysis			
Each additional vial of PVA	5.68	2.05-15.75	0.001
HIGH NRS-SCORE (≥ 5) n=24			
Univariate analysis			
Each additional vial of PVA	1.965	1.08-3.58	0.027
Creatine kinase (>170 U/l)	2.69	0.86-8.37	0.088
Multiple analysis			
Each additional vial of PVA	1.965	1.08-3.58	0.027

*[1] SIR: Society of Interventional Radiology; *[2] NRS: Numerical Rating Scale; *[3] 95%CI: 95% Confidence Interval

93.36). Smaller uterine volumes were found to be associated with smaller diameters of the uterine artery (left: p=0.001, right: p=0.01). We found no association between technical failures and the following: previous treatment, color doppler-flow characteristics of the dominant fibroid, T_2-signal intensity of the dominant fibroid, the location of the dominant fibroid, anatomical variation and diameter of the uterine artery and the pre-procedural use of GnRH analogues.

No specific risk factors were identified for the occurrence of vasospasm. Especially the prior use of GnRH analogues, anatomic variations or the diameter of the uterine artery were not associated with an increased risk of spasm.

For the onset of fever (>38.5°C/101.3°F) following the procedure until 6 weeks afterwards, several covariates showed a significant association in the univariate analysis: a short procedural time (0-75 min) (OR: 3.86; 95%CI: 1.01-14.69) and the total number of PVA vials used (OR: 2.17; 95%CI: 1.15-4.11). In the multiple analysis, however, only the amount of PVA used was found to be positively correlated with fever (OR: 2.05; 95%CI: 1.09-3.87; p=0.027). Post-intervention fever occurred more often in patients who received prophylactic antibiotics but the difference was not significant (27.6% versus 21.2%; OR: 1.42, 95%CI: 0.44-4.58; p=0.512).

For the SIR-defined minor complications (Class A and B) from the procedure until 6 weeks afterwards, no significant association was found with any covariate. Analysis of the occurrence of at least one SIR-defined major complication (Class C, D, E and F), however, indeed revealed some positive associations (Table 6). Again the amount of PVA used was associated with a higher risk (OR: 5.68; 95%CI: 2.05-15.75). This was also the case for a large uterine volume (OR: 3.97; 95%CI: 1.12-14.09), a large volume of the dominant fibroid (OR: 4.57; 95%CI: 1.24-16.86) and an increased creatine kinase level one day after UAE (OR: 3.77; 95%CI: 1.01-14.05). The multiple analyses showed that the risk for major complications was significantly increased with each extra vial PVA used (OR: 5.68; 95%CI: 2.05-15.75).

High pain scores (i.e. NRS > 5) also positively associated with the amount of PVA used in both univariate and multiple analyses (OR: 1.97; 95%CI: 1.08-3.58). No association was found between high pain scores and uterine size, dominant fibroid size, or total number of fibroids.

DISCUSSION

This paper reports the technical results of UAE performed as part of a multicentre, randomized controlled trial.

Failed procedures occurred in 14/81 women (17%), with a technical failure rate of 5.3% (i.e. the impossibility to embolize 8/152 present arteries). We found two risk factors to be strongly associated with failed procedures: the presence of a single fibroid and a small uterine volume: OR: 6.21 (95%CI: 1.65-23.4; p=0.007) and OR: 10.8 (95%CI: 1.25-93.4; p=0.03) respectively. The relatively small caliber of the uterine artery under these circumstances is the common biological explanation for the increased risk of procedural failures in these women. Since the number of fibroids and the uterine volume can be identified

well before the intervention, this information should be used in counseling. Several case reports suggest prior use of GnRH analogues as a risk factor for procedural failure. Although we found in our analysis no association between GnRH analogues and procedural failure, 3 of the 5 patients, who had stopped using GnRH analogues less than 60 days before the UAE procedure, turned out uni- or bilateral failures.

We found the occurrence of post-procedural fever (>38.5°C/101.3°F) and other post-procedural complications to be significantly associated with the amount of embolization material used, i.e. the number of PVA-vials. The occurrence of fever doubled (OR: 2.05; 95%CI: 1.09-3.87; p=0.027), while the occurrence of other complications was increased five-fold (OR: 5.68; 95%CI: 2.05-15.75; p=0.001) with each additional vial of PVA that was used. As might be expected, large uterine size (>500 cc) and a large dominant fibroid volume (>100 cc) were also associated with an increased risk of fever and other complications in the univariate analysis, but the amount of PVA vials turned out being the sole responsible risk factor in the multiple analysis.

Accordingly, we found a strong association between the amount of embolization material used and high pain scores (OR: 1.9; 95%CI: 1.09-3.58; p=0.027).

Again, large uterine- and dominant fibroid volumes were found to be associated with high pain scores in the univariate analysis, as was a high post-intervention level of creatine kinase (>170 U/l), being a marker of damaged tissue. Only the amount of PVA used stood out in the multiple logistic regression analysis, however, once more confirming a dose-effect relationship.

Our technical failure rate (5.3%) was higher than those reported in some large case series (0.5-3%), but similar to those found by others [17]. Our study was performed in a multi-center setting instead of a single highly specialized center, which may have inflated our failure rate. However, this arguably also increases the generalizability of our findings. In our study the procedures were performed by intervention radiologists with variable levels of experience in UAE, but all had ample experience in other embolization procedures. We were unable, however, to disclose any association between experience levels and the occurrence of failed procedures. Another reason for the higher procedural failure rate is the higher number of single sided uterine arteries 10/81 (12.3%) observed in our study when compared to previous reports [18;19].

The main reason for technical failures in our study was difficulties in catheterizing small or tortuous arteries. This has also been reported by others with reported incidences of 0.7-5% [3;17;18;20;21]. The incidence of vasospasm as a cause for technical failure was much lower in our study than in previous reports. Only in two arteries (2/162; 1.2%), spasm resulted in definite technical failures, while others report vasospasm as a significant problem in 10%

and 26% of procedures [6;22]. In concordance with another report, we found types III (35.2%) and I (29%) to be the most common anatomical variation. Gomez et al. [13] observed type I in 45%, type II in 6%, type III in 43% and type IV in 6% of patients. We did not find any association between the anatomical type and failed procedures.

There are some limitations to our study which need to be addressed. Firstly, as the inclusion criteria indicate, we only included patients with menorrhagia as predominant symptom (with or without bulk-related symptoms and/or pain) excluding patients with only bulk-related symptoms without menorrhagia. At study onset (2001), reported cure rates of UAE ranged from 80-90% in case of menorrhagia to approximately 60% in case of bulk-related symptoms [23]. At that time, therefore, we considered UAE not to be a viable treatment option for patients with bulk-related symptoms as their only problem. As our results show, however, the majority of included patients had a mix of menorrhagia and bulk-related symptoms (135/177, 76.3%).

Secondly, the classification of small, normal, wide for the uterine artery vessel size as used in this trial was based on the judgment by the interventional radiologist who performed the procedure, not on any quantative measurement. We are aware that this is not a validated way to describe the vessel, but we are convinced that experienced interventional radiologists were able to give a good estimate of the vessel size.

Thirdly, our results differ in some aspects with those from earlier studies, and in fact, are worse. An explanation is provided by the following characteristics of our study. In contrast to other studies, our data were gathered prospectively, in a RCT with meticulous data-monitoring and follow-up. We entered patients at a point in time where hysterectomy had become an acceptable treatment modality, which indicates that our study population probably represents a different subset from the clinical spectrum than those women treated in other series.

Despite the large amount of case series published on UAE [3;5;17;18;22-25], none, except one, has focused on the systematic evaluation of complications. Our study provides a full account of complications occurring up to 6 weeks after the procedure, thereby using the standard SIR classification system. Only Spies et al. have previously reported complications similarly [26] . They reported 10 minor in-hospital complications in 400 consecutive patients (2.5%), considerable lower than the 28.4% in our study. Intraprocedural complications were rare (7.4%) in our study. We only encountered minor complications; especially perforations and allergic reactions were not observed. The overall incidence of groin hematomas was relative high, because any swelling or coloring of the groin was reported in the case record form as a hematoma. However, none of the groin hematomas needed any intervention, indicating that it was a frequent, but only minor complication.

Other studies report similar or higher complication rates. One large case series reported an overall procedural complication rate of 5.3% (30 of 555) with 3 major complications resulting in extra care or an extended hospital stay [27]. A randomized trial reported 11 complications in 10/40 (25%) UAE patients [28].

Our most common complication requiring re-hospitalization was febrile morbidity and persistent pain, while Spies et al. reported fibroid tissue passage as the most common reason for readmission [26]; this only occurred once in our 6 weeks follow-up. Spies et al. reported a similar readmission rate to ours (10.5% versus 11.1%) [26], although another large case series reported a lower readmissions rate (16/555; 3%) [27]. In contrast with other studies no emergency hysterectomies within 6 weeks after UAE were performed in our study. One large case series reported 3 infectious complications leading to hysterectomy (3/400) [4], while another described one post-UAE infection needing hysterectomy (1/167) [3]. A Canadian case series reported 8 women (8/555) that underwent complication-related hysterectomy in a 3 months follow-up study [29]. It remains unclear if these complicated cases were associated with the use of large quantities of embolization material.

Only few reports address the risk factors of complications. Spies et al. analyzed only for race and age, but found no association with complications [26]. McLucas et al. found no association between the presence of fever and the number of vials used, the particle size used or the pre-UAE volume of the uterus, but his number of patients with fever was lower than in our study [3]. Rajan et al. retrospectively found no association between the occurrence of (intrauterine) infectious complications and the location of the dominant fibroid, the embolic agent, the quantity of embolic agent or the use of antibiotic prophylaxis [30]. We found a significant and strong dose-response effect between the amount of embolization material used and occurrence of fever and other complications.

As suggested by this finding, it seems likely that by using too much embolization material, serious complications may ensue. Although no life threatening complications were met in our study, this notion is illustrated by a case report of a fatal sepsis following UAE where 12 vials of microspheres were used [31]. It is a clinical reality, that larger dosages of embolization material are required whenever larger uteri and/or larger fibroids are being embolized, in order to obtain satisfying results in terms of symptomatic relief. It seems likely, however, that a balance must exist between the long term objective of symptomatic relief and the occurrence of short term dose-related complications.

We observed 7 patients experiencing hypertension promptly after UAE, which, fortunately, did not lead to major complications. Interestingly, others have also observed this, albeit less frequently, but with 3 emergency room returns and 1 readmission among these unfortunate

women [32]. We have no proper explanation for these findings, but the release of vaso-active substances or mere pain may be involved, and need further study.

In summary, our findings demonstrate that women with relatively small uterine volumes or with a single fibroid are at a higher risk for procedural failure and probably should be counseled accordingly. Radiologists should be aware of the dose-response effect between the number of vials of PVA used, and the risk of complications and pain. As a consequence, whenever more embolization material is used, patients should be monitored more closely in anticipation of severe pain and complications.

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4

PAIN AND RETURN TO DAILY ACTIVITIES AFTER UTERINE ARTERY EMBOLIZATION AND HYSTERECTOMY IN THE TREATMENT OF SYMPTOMATIC UTERINE FIBROIDS: RESULTS FROM THE RANDOMIZED EMMY TRIAL

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ABSTRACT

Background

A randomized controlled trial was conducted to evaluate the safety and efficacy of uterine artery embolization (UAE) and hysterectomy for symptomatic uterine fibroids. The present paper analyses short-term outcomes, i.e. pain and return to daily activities.

Methods

Patients were randomized (1:1) to UAE or hysterectomy. Pain was assessed during admission and after discharge, both quantitatively and qualitatively using the numerical rating scale and questionnaires. Time to return to daily activities was assessed by questionnaire.

Results

75 patients underwent hysterectomy and 81 patients UAE. UAE patients experienced significantly less pain during the first 24 hours after treatment ($p=0.012$). Non-white patients had significantly higher pain scores. UAE patients returned significantly sooner to daily activities than hysterectomy patients (for paid work: 28.1 versus 63.4 days; $p<0.001$).

Conclusion

In conclusion, pain appears to be less after UAE during hospital stay. Return to several daily activities was in favor of UAE in comparison to hysterectomy.

INTRODUCTION

Uterine artery embolization (UAE) is increasingly popular for the treatment of symptomatic uterine fibroids. UAE was first described in 1995 [1]. Present knowledge on UAE mainly derives from several large uncontrolled case series [2-6]. Although some consider UAE as a treatment with proven efficacy, most authors feel that more evidence is required [7-9]. Recently we published the first results from our prospective, multi-centre, randomized controlled trial comparing UAE with hysterectomy for the treatment of menorrhagia caused by uterine fibroids [10]. Overall complication rates were comparable in both treatments.

Although hysterectomy is 100% effective in treating menorrhagia complaints, which is impossible for UAE, some disadvantages are present too. Recovery after hysterectomy is typically lengthy and pain after abdominal surgery can be severe. UAE might provide some advantages over hysterectomy when it comes to pain and recovery. In a previously published small randomized trial UAE patients recovered significantly earlier than hysterectomy patients [11]. A comparison of pain has never been made in a randomized trial before.

The present paper focuses on the comparison of post-interventional pain and return to daily activities between UAE and hysterectomy.

METHODS

STUDY DESIGN

The EMMY (EMbolization versus hysterectoMY) study is a multi-centre randomized controlled trial, conducted in the Netherlands in 5 teaching and 29 non-teaching hospitals. A detailed description of the study has been provided elsewhere and is summarized here briefly [10].

Patients were included if: 1) uterine fibroids had been diagnosed clinically, and confirmed by ultrasonography , 2) menorrhagia was the predominant complaint, 3) they were to be scheduled for a hysterectomy, 4) they were pre-menopausal, 5) preservation of the uterus was not warranted for future pregnancy, 6) the following disorders were absent: moderate or severe renal failure (creatinine > 150 mmol/L), active pelvic infection, clotting disorders, contrast fluid allergy, (suspected) uterine malignancy, submucosal fibroids with >50% of their diameter within the uterine cavity or pedunculated serosal fibroids.

After written informed consent had been obtained computerized randomization was carried out, assigning patients 1:1 to either UAE or hysterectomy, stratified for each hospital.

No power calculation was done for the analysis presented in this paper.

TABLE 1A. Baseline characteristics

	UAE n=88 n (%)	Hysterectomy n=89 n (%)
Age (years)		
Mean (SD)	44.6 (4.8)	45.4 (4.2)
Body Mass Index (BMI) (Weight (kg) / length $(m)^2$)		
Mean (SD)	26.7 (5.6)	25.4 (4.0)
Parity		
0	30 (34.1)	20 (22.5)
≥ 1	58 (65.9)	69 (77.5)
Ethnicity		
Black	24 (27.3)	20 (22.5)
White	54 (61.4)	57 (64.0)
Other	10 (11.4)	12 (13.5)
Highest educational level		
Elementary school	3 (3.4)	6 (6.9)
Low level (Lower vocational, lower secondary school)	29 (33.0)	32 (36.8)
Medium level (Intermediate vocational, higher secondary school)	26 (29.5)	27 (31.0)
High level (Higher vocational/College/University)	28 (31.8)	22 (25.3)
Other	2 (2.3)	0 (0)
Current smoking		
Yes	21 (23.9)	23 (25.8)
No	67 (76.1)	66 (74.2)
Previous treatment		
Hormonal	59 (67.0)	59 (66.3)
Non hormonal (NSAID*[1]/Tranexaminic acid)	45 (51.1)	41 (46.1)
Iron-supplement/blood transfusion	50 (56.8)	52 (58.4)
Surgical (one or more)	17 (19.3)	11 (12.4)
None	11 (12.5)	15 (16.9)
Symptoms		
Menorrhagia	88 (100)	89 (100)
Pain during menstruation	47 (53.4)	50 (56.2)
Urinary symptoms	13 (14.8)	20 (22.5)
Defecation problems	5 (5.7)	5 (5.6)
Anemia	43 (48.9)	42 (47.2)
Comorbid disease*[2]	24 (27.3)	22 (24.7)
Duration of symptoms (months)		
Median (range)	24 (3-250)	24 (4-240)
Number of fibroids		
1	35 (39.8)	25 (28.1)
2	13 (14.8)	16 (18.0)
3	17 (19.3)	25 (25.8)
>3	18 (20.5)	14 (15.7)
Median (range)	2 (1-20)	2 (1-9)
Uterine volume (cm^3)		
Mean (SD)	471.9 (449.9)	483.5 (511.4)
Fibroid volume (dominant fibroid, cm^3)		
Mean (SD)	121.5 (150.4)	159.0 (266.2)

*[1] Non-Steroidal-Anti-Inflammatory-Drugs; *[2] At least one of the following: hypertension; diabetes; asthma; systemic disease

According to the Dutch national guidelines the study was approved by the Central Committee Involving Human Subjects (www.ccmo.nl) and by the local ethics committees of all participating hospitals.

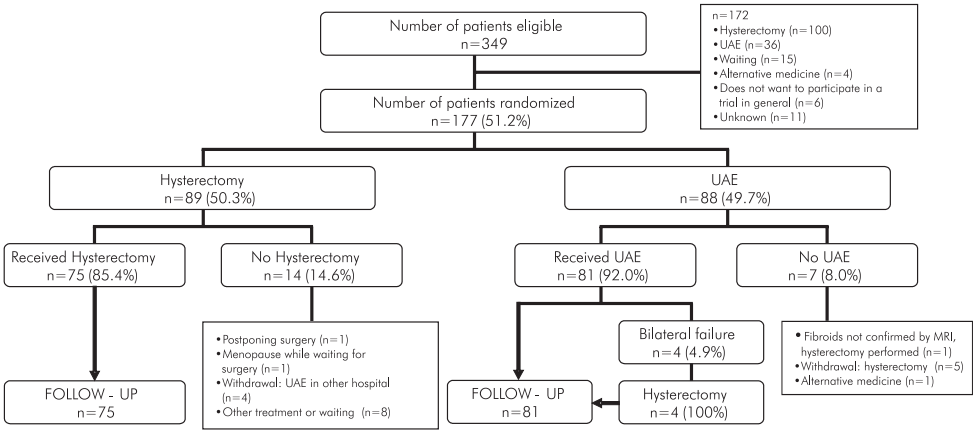
Between March 2002 and February 2004 a total of 177 patients participated in the study: 88 patients were randomly allocated UAE and 89 patients hysterectomy. Their baseline characteristics are listed in Table 1A. In the UAE group 81 patients underwent the procedure, compared to 75 in the hysterectomy group; the remaining patients refused the allocated treatment and withdrew from the trial. The flow of patients is visualized in Figure 1.

Before treatment a gynecological and general medical history was taken and patients underwent an ultrasound assessment of the uterus to determine the size of the uterus, the size of the largest fibroid and the total number of fibroids. A laboratory work-up included hemoglobin level. Patients filled out a questionnaire comprising various quality of life issues.

TABLE 1B. Procedural characteristics

		UAE n=88 n (%)	Hysterectomy n=89 n (%)
Type of UAE			
Target embolization	Left uterine artery	65	-
	Right uterine artery	59	-
Selective embolization	Left uterine artery	8	-
	Right uterine artery	12	-
Type of hysterectomy			
Abdominal hysterectomy		-	63
Pfannenstiel incision		-	50
Median incision		-	13
Vaginal hysterectomy		-	8
Vaginal hysterectomy with morcellator		-	1
LH with morcellator		-	2
LAVH		-	1
Anesthesia			
Local		71	-
Epidural		9	1
Spinal		1	3
General anesthesia		-	52
General and epidural		-	17
General and spinal		-	2
Duration of procedure (min)			
Mean (SD)		79 (30)	95 (30)
Median (range)		75 (30-165)	90 (45-175)
Amount of PVA used			
Mean (SD)		1.85 (0.87)	-
Median (range)		2.0 (0.5-5.0)	-

FIGURE 1. Trial profile



UTERINE ARTERY EMBOLIZATION

UAE was performed under local anesthesia. Polyvinyl alcohol particles (PVA, Contour, Boston Scientific, Beek, The Netherlands) with a size of 355-500 μm were used in all procedures. Only if an anastomosis with the ovarian artery was observed, 500-700 μm particles were used. Embolization was carried out until parenchyma filling of the fibroids had stopped (target embolization) or until the main uterine artery was blocked with stasis of contrast (selective embolization).

The type of anesthesia and the use of analgesics was not standardized, but was recorded in the standardized case record form. After the procedure women were admitted to the gynecology ward for post procedural care. All patients were advised to stay in the hospital for one night.

HYSTERECTOMY

The type of hysterectomy and the route of access were left at the discretion of the attending gynecologist and comprised abdominal, vaginal or laparoscopic procedures. Both supravaginal and total hysterectomies were allowed. The type of anesthesia and the use of analgesics were not standardized, but recorded in the case record form. Procedural characteristics were recorded.

SHORT TERM RESULTS

Table 1B lists the procedural characteristics in the two groups. Bilateral UAE was impossible in 4/81 patients (4.9%) for the following reasons: bilateral absence of uterine artery flow to the fibroids (n=2), bilateral technical failures (n=1) and extensive anastomoses with the cervix/vagina on one side and a technical failure on the other (n=1). These four patients subsequently underwent hysterectomy, but were analyzed in the UAE group [10].

Unilateral UAE was carried out in 10/81 patients (12.3%). These failures were due to: unilateral absence of the uterine artery (n=5) and unilateral technical failure (n=5).
In the hysterectomy group an abdominal hysterectomy was performed in 64/75 cases (85.3%; 50 pfannenstiel and 13 median laparotomies), while 10 women underwent a vaginal hysterectomy (13.3%; including 1 LAVH and 1 procedure with morcellation). Furthermore 2 laparoscopic hysterectomies were performed (2.7%). Total admission time (discharge date minus admission date) significantly differed between the UAE group and the hysterectomy group (mean: 2.0 days versus 5.1 days; $p<0.0001$) [10].

PAIN CONTROL AND ASSESSMENT

Pain intensity was assessed using the numerical rating scale (NRS) at the following time points: before treatment (< 24 hours); 1, 3, 6 and 24 hours after treatment [12]. At these time-points, the attending nurse asked patients to indicate their actual pain score on a scale ranging from 0 ('no pain') to 10 ('worst pain imaginable') by circling the appropriate number on the scale. When a patient was asleep, un- or subconscious, this was recorded and no score was obtained. NRS scores were assessed only during hospitalization. Since this report focuses on the comparison between UAE and hysterectomy, NRS scores were only obtained during the first 24 hours, since both groups were still hospitalized in this period.
As no pain regimen protocols were compulsory in the study, various analgesic measures were used: epidural anesthesia; opiates; paracetamol; non-steroidal anti inflammatory drugs (NSAIDs) or a combination. All analgesics used before, during, and after the procedure until discharge were recorded. For analysis of peri-procedural pain, analgesic regimens were subdivided into three subgroups: tablets only (paracetamol and/or NSAIDs); opiates (with or without paracetamol and/or NSAID tablets) and epidural anesthesia. Patients were discharged from the hospital when their physical condition allowed so, while pain was controllable by the administration of paracetamol and/or NSAIDs.
Duration of pain after discharge was assessed at the first follow-up visit 6 weeks after discharge. Patients were asked how long (days) pain had lasted after discharge. The use of any analgesics during the 6 weeks period after discharge was recorded.

RETURN TO ACTIVITY

Six weeks after discharge, return to daily activities was assessed by means of a questionnaire, inquiring how many days after hospital discharge women had refrained from the following activities: paid work, voluntary work, doing groceries, usual household activities, heavy household activities, resuming leisure time activities and resuming activities with children.

Whenever 'not yet' was answered, the question was repeated in the next (6 months) follow-up questionnaire.

STATISTICAL ANALYSIS

Data entry was performed using SPSS data entry for Windows 3.0. All data entries were visually double checked by an independent second investigator. Analysis was done using SPSS statistical software (version 11.5.1). Study outcomes were analyzed according to the original treatment assignment (intention to treat) unless stated otherwise.

NRS-scores of patients were included in the analysis when maximally one value was missing. In that case a mean value for non-missing responses was used (for each group separately).

Differences in follow up NRS scores between groups were calculated with a Mann Whitney U test (for non-parametric values) or a Student's t-test (for parametric values).

Differences in longitudinal pain score patterns between the two groups were measured using mixed models linear regression analysis. In this analysis the baseline characteristics mentioned in Table 1A and intended treatment (UAE/hysterectomy) were included for multiple regression analysis, whenever univariate analysis revealed p-values < 0.1. Furthermore, post-procedural pain scores were averaged (until 24 hours after treatment) and dichotomized for scores $>$ or < 5. Logistic regression analysis was performed with these categories as dependent variables, to identify baseline factors associated with above average pain-scores. For this analysis the same variables were used as for the repeated measures analysis described above. Patients receiving elective epidural anesthesia were excluded from this analysis.

Differences in average number of days until return to activities were calculated by Student's t-tests. Differences in the time to return to various activities were calculated by log-rank tests.

For each activity multiple linear regression analysis was performed separately as follows. First univariate linear regression analysis was performed to identify baseline factors that influenced time to return to activities. The baseline factors in Table 1A were studied together with intended treatment (UAE/hysterectomy). For this analysis all factors were dichotomized. Co-variables with p-values <0.1 in the univariate analysis, including significant interaction terms, were studied in a multiple linear regression analysis. This resulted in Beta values for all variables that were statistically significant in the multiple regression analysis. The Beta-value represents the reduction in time to return to activities expressed in days for the reference category of the variable. Adjusted R^2 (goodness of fit) were calculated to evaluate the proportion of variance explained by the model.

Finally, in the UAE group, a regression analysis was performed to study the impact of the attending interventional radiologist's previous experience with UAE (i.e. those who had done >10 or <10 UAE procedures) on patients' pain scores and recovery time.

Differences for categorical data were compared with χ^2-tests or Fisher exact tests if appropriate. A p-value of <0.05 was considered statistically significant. Since procedural characteristics differ in both groups (different types of hysterectomy and uni/bilateral UAE) we repeated the analyses on differences in NRS-scores and return to activities for two subgroups of patients: bilateral UAE versus abdominal hysterectomies.

RESULTS

Pain-scores were available for 135 patients (UAE: n = 77; hysterectomy: n = 58).

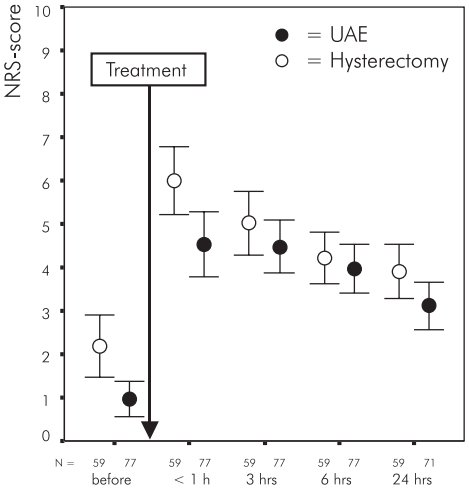
Hysterectomy patients reported significantly more pain at 1 hour after treatment (UAE: 4.54; hysterectomy: 6.03; p=0.008) (Figure 2).

During the first 24 hours after treatment, hysterectomy patients had significantly higher pain scores in the repeated measures analysis (p=0.012). Only white ethnicity was significantly associated with lower pain scores (estimate (Beta): -1.16, 95%CI: -2.10 to -0.23; p=0.015) in the univariate analysis of baseline factors.

Average pain scores during hospitalization > 5 occurred in 24/77 (31.2%) in UAE versus 30/58 (51.7%) in hysterectomy patients (RR: 0.59; 95%CI: 0.39-0.89; p=0.012). No baseline factors were identified that predicted high (>5) average pain scores.

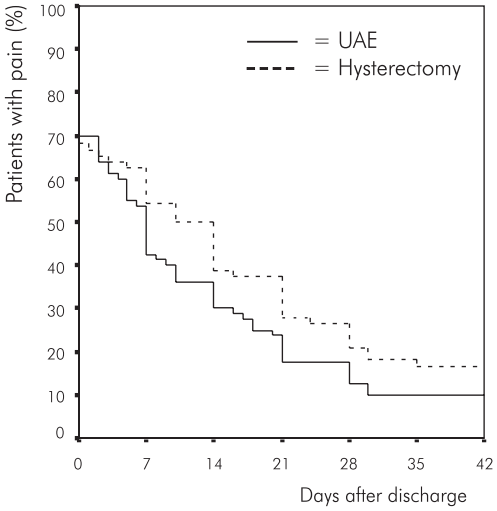
Experienced interventional radiologists did not have significantly more patients with high average pain scores than less experienced colleagues (OR: 1.32; 95%CI: 0.45-3.89; p=0.60).

FIGURE 2. Pain before and after treatment



Presented data are means (dots) and the standard error of the mean (line)

FIGURE 3. Pain after discharge



Detailed medication descriptions were available for 140 patients (UAE: 72; hysterectomy: 69) (Table 2). The majority of patients in both groups needed opiates at one point during the first 24 hours as strongest analgesic. In both groups, patients who received opiates had the highest pain scores, except for three patients in the UAE group who needed secondary epidural anesthesia, because of unbearable pain despite the administration of opiates.

Six weeks after discharge, 57 UAE patients reported to have experienced pain after discharge compared to 52 hysterectomy patients (70.4% versus 69.3%, p=0.89). After 6 weeks 8 patients (9.9%) still reported pain in the UAE group compared to 12 patients (16.0%) in the hysterectomy group (p=0.25). In the UAE group 10 patients (12.3%) still used analgesics compared to 14 patients (18.7%) in the hysterectomy group (p=0.27). Figure 3 displays Kaplan Meier curves for the presence of pain. The difference was not significant (log rank test: p=0.13). The time for 50% of patients to become free from pain after discharge was 7 days (95%CI: 5-9 days) for UAE patients compared to 10 days (95%CI: 6-14 days) for hysterectomy patients. When only bilateral UAE and abdominal hysterectomy were compared, no different results were obtained for the evaluation of pain.

Figure 4 shows Kaplan Meier curves for the resumption of various daily activities over time. All differences between UAE and hysterectomy were statistically significant (p<0.01). Table

TABLE 2. Analgesics used

	UAE (n=72) Average pain		Hysterectomy (n=68) Average pain	
Analgesic measures*1	n	score (SD)	n	score (SD)
Tablets*2 only	15	2.8 (2.0)	5	5.4 (2.7)
Opiates	46	4.8 (1.4)	43	5.4 (1.2)
Epidural anaesthesia	8	2.3 (1.9)	20	2.9 (2.2)
Secondary epidural*3	3	5.5 (0.4)	0	NA

*1 from before until 24 hrs after treatment; *2 Paracetamol and/or NSAIDs; *3 applied after treatment, because of unbearable pain; NA= not applicable

TABLE 3. Time to return to various activities

Activity	UAE Mean (SD) days	Hysterectomy Mean (SD) days	Difference (95%CI)	p-value
Paid work	28.1 (25.7)	63.4 (33.2)	35.3 (24.2-46.4)	<0.001
Voluntary work	16.6 (8.9)	46.6 (30.1)	30.0 (6.4-53.6)	0.016
Usual household activities	12.0 (12.4)	29.0 (30.1)	17.0 (9.7-24.3)	<0.001
Heavy household activities	20.7 (15.4)	53.7 (30.8)	33.0 (25.0-41.0)	<0.001
Doing groceries	14.0 (12.1)	35.0 (30.2)	31.0 (13.8-28.2)	<0.001
Doing things around the house	18.9 (14.4)	39.8 (24.7)	20.9 (14.0-27.8)	<0.001
Leisure time activities	14.8 (13.3)	40.4 (40.1)	25.6 (15.6-35.6)	<0.001
Activities with children	17.4 (14.2)	30.3 (20.6)	12.9 (5.4-20.4)	0.001

FIGURE 4. Return to various activities after hospital discharge

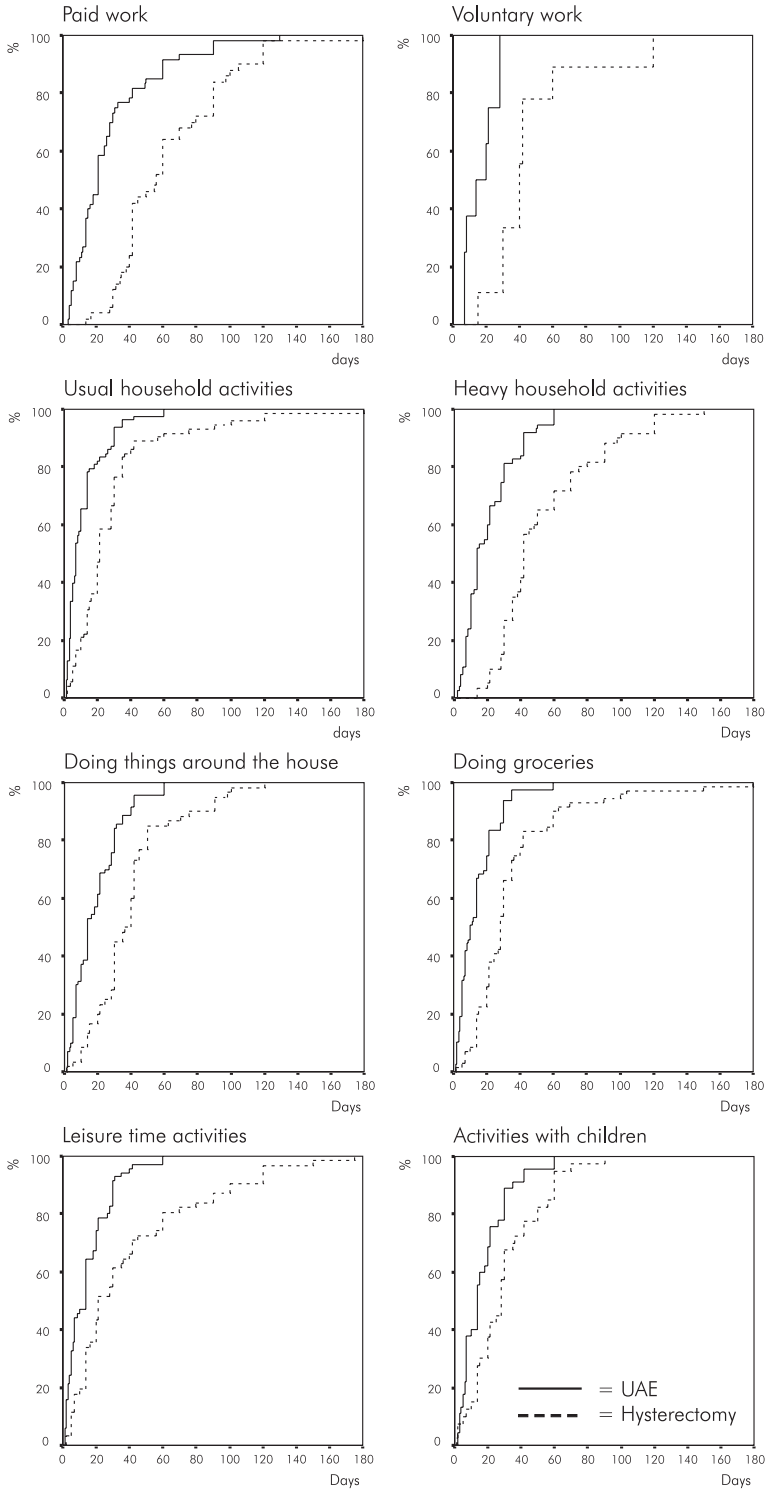


TABLE 4. Factors associated with an earlier return to activities (Beta)

Activity	Beta (days)	95%CI	p-value	Adjusted R^2
Paid work				
Intended treatment (embolization=1)	-41.2	-51.2 to -31.2	<0.0001	0.46
BMI*[1] (<30=1)	-15.9	-28.4 to -3.3	0.014	
Parity (no children=1)	-12.4	-22.7 to -2.2	0.018	
Highest educational level (medium=1)	-14.7	-24.8 to -4.6	0.005	
Supplement therapy*[2] (no=1)	-13.2	-23.2 to -3.3	0.009	
Duration of menorrhagia (>2 years=1)	-17.9	-27.6 to -8.2	0.0004	
Voluntary work				
Intended treatment (embolization=1)	-29.9	-53.6 to -6.3	0.016	0.28
Usual household activities				
Intended treatment (embolization=1)	-16.8	-23.9 to -9.6	<0.0001	0.16
Caucasian ethnicity (yes=1)	-11.0	-18.4 to -3.6	0.004	
Heavy household activities				
Intended treatment (embolization=1)	-34.4	-41.7 to -26.6	<0.0001	0.41
Supplement therapy*[2] (no=1)	-11.4	-19.0 to -3.9	0.003	
Duration of menorrhagia (>2 years=1)	-12.1	-19.7 to -4.4	0.002	
Doing groceries				
Intended treatment (embolization=1)	-21.7	-28.7 to -14.7	<0.0001	0.24
Caucasian ethnicity (yes=1)	-11.3	-18.6 to -4.1	0.002	
Duration of menorrhagia (>2 years=1)	-8.2	-15.3 to -1.1	0.023	
Doing things around the house				
Intended treatment (embolization=1)	-20.0	-26.6 to -13.5	<0.0001	0.30
Highest educational level (medium=1)	-7.9	-15.0 to -0.7	0.032	
Duration of menorrhagia (>2 years=1)	-6.7	-13.3 to -0.1	0.046	
Caucasian ethnicity and comorbid disease (both yes=1)*[3]	-15.7	-25.5 to -6.0	0.002	
Leisure time activities				
Intended treatment (embolization=1)	-25.3	-35.2 to -15.4	<0.0001	0.18
Having had hormonal medication (yes=1)	-12.3	-23.0 to -1.6	0.024	
Activities with children				
Intended treatment (embolization=1)	-13.2	-20.5 to -5.9	0.001	0.16
Supplement therapy*[2] (no=1)	-8.6	-15.9 to -1.4	0.021	

*[1] BMI: body mass index; *[2] Pre-treatment iron-supplement/blood transfusion; *[3] interaction term: both factors have to be positive. Beta values represent the number of days gained in returning to various daily activities when '1' applies to the patient

3 lists the average number of days after hospital discharge required to resume activities for patients in both groups. All differences were statistically significant in favor of UAE.

Multiple regression analysis revealed several variables to be significantly associated with recovery (Table 4). The Beta value in this table represents the reduction of time to return to activities in days. For the activity 'work' this means for example that a patient without children (the reference category), recovered on average 12.4 days earlier than a woman with children (the other category). After adjustment for these variables, UAE patients still

resumed all activities earlier than hysterectomy patients (Table 4): paid work: 41 days earlier; voluntary work: 30 days; usual household activities: 17 days; heavy household activities: 34 days; doing groceries: 22 days; doing things around the house: 20 days; leisure time activities: 25 days; and activities with children: 13 days. R^2 values were moderate to low indicating a high variance within groups.

When differences in return to activities were compared for the abdominal hysterectomy subgroup and the bilateral UAE subgroup, only the difference in return to voluntary work was no longer statistically significant ($p=0.09$). The other differences remained statistically significant ($p<0.01$). In the UAE group experience of the interventional radiologist was not associated with time to return to activities (for all activities: $p>0.10$).

DISCUSSION

This report compares pain and return to daily activities between UAE and hysterectomy. Less pain and early recovery are well known advantages which have been used to promote UAE, however, this claim has only minimal evidence based backup. Only one small semi-randomized trial has demonstrated that recovery is faster after UAE compared to hysterectomy [11]. However, this was a pre-consent randomized trial of moderate quality, with many cross-overs, possibly biasing their results.

The present trial was not designed to study the optimal analgesic regimen, and in practice opinions on this subject vary widely, both for UAE and hysterectomy. Especially for UAE, many analgesics protocols have been described varying from standard epidural anesthesia in all patients, to extensive medication regimens with patient controlled analgesia in combination with NSAIDs [13,14]. Even general anesthesia has been advocated by some authors [15]. As confirmed by our results, pain is an acknowledged problem, both after hysterectomy and after UAE. Pain management should be discussed before intervention, with clear instructions for the patient as to what to expect and what to do when pain increases. Based on our results the occurrence and intensity of pain are unpredictable and should be assessed on a regular basis during admission to enable the administration of analgesics before progression to a level where pain control is virtually impossible [16]. While some patients will do fine on paracetamol, a few will need epidural anesthesia. Because of this variation in pain score results we conclude that a fixed pain medication protocol can not be recommended based on our results. In our trial virtually all patients experienced pain during admission and a substantial proportion of patients had high average pain scores, indicating insufficient pain control. Patients who needed opiates as strongest analgesics also showed the highest

average pain scores. This is probably explained by the fact that opiates were predominantly administered when pain was severe. Epidural anesthesia resulted in the lowest average pain scores, but the invasiveness, complexity, and risks of the procedure restrict its use in daily practice. Since some patients experience no pain at all or only mild pain, which is well controlled by tablets only, treating everyone with epidural anesthesia would result in overtreatment of a considerable number of patients. In our opinion epidural anesthesia for UAE should be applied cautiously and we advocate that everyone should be treated with a combination of tablets and opiates on demand during the first 24 hours. After this, note should be made whether a patient has acceptable pain without the need for opiates. If so, a patient can be sent home with a prescription of oral pain medication and a clear instruction on how to use them. Because we found, as others did, that opiates were administered in a high percentage of patients after UAE, in our study as high as 63.8%, we do not consider UAE as an out patient procedure, as has been advocated in some publications [17;18].

Of course the present study would have been stronger when a standard medication regimen would have been used. However, this was impossible because of the large amount of participating hospitals, each with their own ideas on pain medication protocols.

Unlike pain in the first 24 hours, the number of days with pain after discharge did not differ significantly between the two groups, stressing that a good pain medication regimen is important after discharge, also for the UAE group. In this way high levels of pain which interfere with recovery, can be avoided [16].

Return to daily activities was significantly shorter after UAE as compared to hysterectomy.

The only previously published randomized trial reported also on this subject [11]. In their series, women returned to routine activities after a mean of 9.5 days for UAE compared to 36.2 days for hysterectomy. Although it is not specified what is meant by 'routine activities', our patients resumed routine activities like doing household and doing groceries around two weeks after discharge for UAE patients and around 5 weeks for hysterectomy. This was slightly longer for UAE and about the same for hysterectomy patients.

Data on this issue derived from other (uncontrolled) case series, showed that our UAE patients resumed paid work approximately two weeks later [14;19;20]. The resumption of routine activities also took more time in our study, although the difference with other reports was less than a week [14;20]. Our hysterectomy patients resumed work earlier than those described in a recently conducted large trial (n=1380): in that study, patients resumed paid work after a mean interval of 95 days after undergoing hysterectomy (in our trial 63.4 days) [21]. Local circumstances related to the type of health- and labor insurance, but also to cultural differences in the perception of illness are important in explaining differences between studies from different

populations or countries. However, obviously these differences do not apply in a randomized trial, where both treatments are being compared within the same population.
In this study, we analyzed return to activity after *discharge* rather than after *treatment*. We did so, because the resumption of daily activities does not apply during hospitalization. If we had decided for the other option, differences between both treatments, which already reached statistical significance, would have increased by an average of 3.1 days.
In conclusion, pain during admission is less after UAE compared to hysterectomy. Pain after UAE is unpredictable and therefore a fixed pain protocol cannot be provided. We were unable to identify patient characteristics indicative for excessively high pain scores. After discharge, no differences were observed in the disappearance of pain between the groups. Resumption of daily activities was much sooner after UAE compared to hysterectomy.

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5

FIBROID EXPULSION AFTER UTERINE ARTERY EMBOLIZATION: COMPLICATION OR CURE?

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ABSTRACT

A 54-year-old woman presented with an expulsed fibroid 10 weeks after UAE. After treatment with antibiotics and a small surgical intervention, she recovered completely without any sign of myomatous disease afterwards.

Patients should be informed about the possibility of expulsion. Expulsion of fibroids after UAE occurs relatively frequently and may be just one of the ways to attain cure.

INTRODUCTION

Uterine artery embolization (UAE) for the treatment of uterine fibroids causing abnormal menstrual bleeding, was first reported by Ravina et al. in 1995 [1]. Their promising results were confirmed in several uncontrolled cohort studies, reporting a decrease in uterine volume of approximately 50% and relief of symptoms in 80-90% of patients [2]. Severe complications like pelvic infection and even death have been reported but seem to be rare. Expulsion of fibroids has also been described as a complication of UAE [2]. In this paper we report one such case.

CASE REPORT

A 54-year-old woman, para 1, consulted our outpatient-clinic with complaints of heavy menstrual bleeding, dysmenorrhoe and anemia (hemoglobin: 6.0 g/dL) She was previously diagnosed with a single uterine fibroid. Several medical treatments failed to give any symptomatic relief. The patient consented to participate in the so-called EMMY (EMbolization versus hysterectoMY)-trial, an ongoing multicentre randomized controlled trial in the Netherlands, to evaluate the effects of uterine artery embolization for the treatment of symptomatic uterine fibroids that cause menorrhagia, compared to hysterectomy. The patient agreed to participate in the study and was randomly allocated to the embolization group.

According to the study protocol an MRI-scan was performed. The uterus measured 12.2 cm × 11.5 cm × 14.1 cm (1035 cm^3, calculated using the formula for prolate ellipsoids: 0.5233 × D1 × D2 × D3). A single submucosal/intramural fibroid, distorting the uterine cavity was confirmed, measuring 10.3 cm × 7.4 cm × 9.8 cm (391 cm^3) (Figure 1A).

Uterine artery embolization was performed under local anesthesia via bilateral femoral artery access using 355-500 μm polyvinyl alcohol particles (Contour, Boston Scientific, Cork, Ireland), 2 vials on the left side and 1 vial on the right side.

After the procedure the patient was admitted to the gynecology ward for observation. She experienced moderate pelvic pain, which was well controlled by paracetamol and non-steroidal-anti-inflammatory-drugs. One intra-muscular injection of opiates was required for optimal pain relief two hours after the procedure. No complications occurred and the patient was discharged from the hospital the next day.

Ten weeks after the procedure the patient contacted us, complaining of labor-like cramps in the lower abdomen, fever (with a temperature up to 39.3°C/103.82°F) and foul-smelling vaginal discharge since three days. Vaginal examination revealed a gray/yellowish malodorous

mass prolapsed through a dilated cervix. At that time it was impossible to remove the necrotic tissue. We prescribed antibiotics (Amoxicilline for 5 days) and arranged for the patient to return for follow up three days later. At this time the myoma protruded from the vagina. On vaginal examination the fibroid was still connected to the inside of the uterus (Figure 2A). Manipulation was very painful and we decided to remove the mass in the Operating Room under general anesthesia. The necrotic fibroid was easily twisted of (Figure 2B) and no fibroid tissue seemed to remain in the uterus. During the procedure antibiotics were admitted intravenously and continued orally thereafter: metronidazol and cefuroxim for 8 days.

Histo-pathological examination of the removed tissue (weight: 131 grams) showed extensive necrosis in what originally appeared to be fibroid tissue.

FIGURE 1. T2-weighted sagittal MRI scan of the uterus before (A) and after (B) removal of the necrotic fibroid

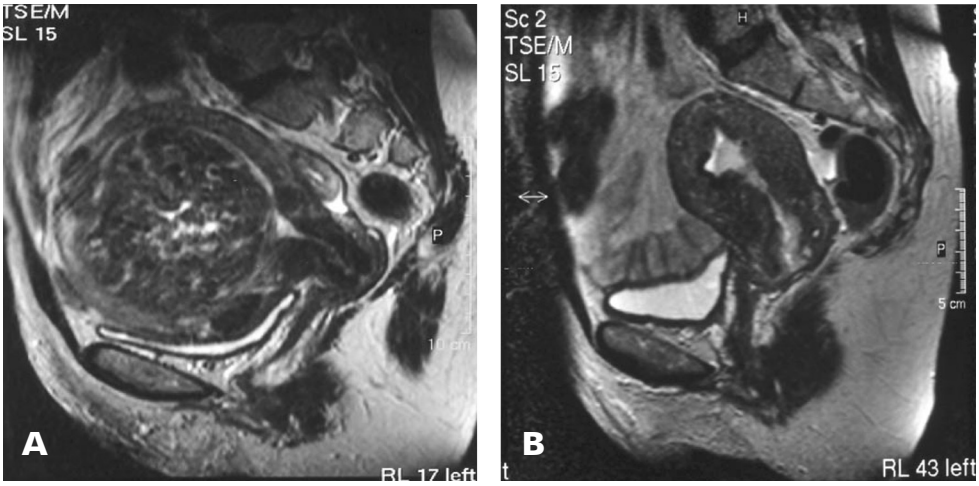
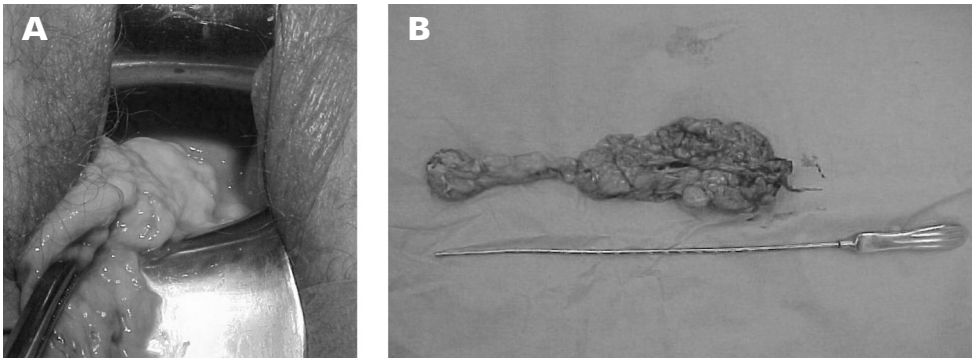


FIGURE 2. Macroscopic appearance of the necrotic fibroid (A) protruding through the cervix (arrow) and (B) after the procedure: measuring 26 cm in length



After removal of the necrotic fibroid both fever and pain disappeared promptly. An MRI-scan performed 4 weeks after removal of the necrotic tissue showed no signs of any fibroid structure anymore (Figure 1B). The uterus measured 7.2 cm x 9.8 cm x 5.8 cm (214 cm^3). The volume reduction was 821 cm^3 (79%) compared to the earlier scan. The first menstruation after the procedure appeared 2 weeks later and was completely normal and without any pain.

DISCUSSION

Fibroid expulsion after UAE occurs relatively frequently. Reported incidences range from 0.5-17.7% [3;4]. After UAE the average shrinkage of the uterus is reported to be 43-58% [2].
Necrotic fibroid tissue is thus either gradually absorbed by the uterine wall itself or (in a minority of cases) expelled as a whole. The question that rises here is therefore: is losing the necrotic (portion of a) fibroid a real complication or simply a much faster cure for this disease, in some cases inevitable to happen? In the case of our patient the anatomy of her uterus was practically restored to normal after expulsion of the fibroid after AUE without the need of major surgery. Her initial symptoms completely disappeared and there was no sign of fibroid disease anymore.
Although the final result can be satisfactory, patients should be informed about the possibility of expulsion and be well monitored to avoid serious infectious complications. This way abdominal hysterectomy may be avoided. In conclusion, fibroid expulsion after UAE is not uncommon and may be just one of the ways to attain cure.

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UTERINE ARTERY EMBOLIZATION **VERSUS** HYSTERECTOMY FOR SYMPTOMATIC UTERINE FIBROIDS

II

LONG TERM RESULTS

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6

UTERINE ARTERY EMBOLIZATION VERSUS HYSTERECTOMY IN THE TREATMENT OF SYMPTOMATIC UTERINE FIBROIDS: TWO-YEARS' OUTCOME FROM THE RANDOMIZED EMMY TRIAL

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ABSTRACT

Objective

The purpose of this study was to compare the 2 years' efficiency of uterine artery embolization (UAE) with hysterectomy in the treatment of menorrhagia caused by uterine fibroids in a randomized controlled trial.

Methods

Twenty-eight Dutch hospitals recruited patients with uterine fibroids and menorrhagia, who were eligible for hysterectomy. Patients were randomized to UAE or hysterectomy. The primary endpoint was if UAE could avoid a subsequent hysterectomy in at least 75% of cases. Secondary endpoints were changes in pain, bulk-related complaints and uterine and dominant fibroid volume reduction.

Results

177 patients were randomized to UAE (n=88) or hysterectomy (n=89). Two years after treatment 23.5% of UAE patients had undergone a hysterectomy. There were no significant differences in improvement compared to baseline in pain and bulk-related complaints. Uterine and dominant fibroid volume reduction in UAE patients was 48.2% and 60.5% respectively.

Conclusion

UAE is a valuable alternative treatment for symptomatic uterine fibroids. Nevertheless when patients seek for certainty on the cessation of bleeding problems, a hysterectomy remains the treatment of choice.

INTRODUCTION

Uterine artery embolization (UAE) for the treatment of heavy menstrual bleeding caused by uterine fibroids was first described in 1995 [1]. Since then several large case series have been published describing benefits and risks of UAE [2-6]. These reports have suggested UAE to have advantages over surgery. Firm evidence for this, however, is hampered by the inclusion of patients with strong treatment preferences for UAE and the lack of a control group of women undergoing alternative treatment, e.g. hysterectomy. Obviously, this affects the validity and generalizability of these reports. Although hysterectomy is an absolute cure for menorrhagia, possible sequelae, e.g. incontinence, vaginal vault prolapse, risk for premature ovarian failure, high costs and the desire of some patients to preserve their uterus, justify serious consideration of an alternative, less invasive therapy such as UAE.

To evaluate the efficacy of UAE in comparison to the standard treatment, i.e. hysterectomy, we initiated a prospective, multi-centre, randomized trial comparing uterine artery EMbolization with hysterectoMY (EMMY trial) for the treatment of menorrhagia caused by uterine fibroids. We previously reported on the short-term results of the EMMY trial [7-9].

The objectives of the present report were to compare UAE and hysterectomy with regard to the primary endpoint of clinical success at 2 years follow-up, and to evaluate the effect of UAE on uterine and dominant fibroid size assessed by ultrasound and MR imaging during this period.

METHODS

STUDY DESIGN

The design and methods of the trial have been described in detail elsewhere [9]. In brief, the EMMY study is a multi-centre, randomized non-inferiority trial conducted in the Netherlands.

Patients visiting the gynecological outpatient clinics were asked to participate if they met the following criteria: 1) the clinical diagnosis of uterine fibroids had been confirmed by ultrasonography; 2) menorrhagia (reported by the patient as increased or prolonged menstrual blood loss causing dysfunction in daily life) was the predominant complaint. Patients who exclusively had bulk-related symptoms and/or pain but no menorrhagia, were not included; 3) patients were premenopausal; 4) hysterectomy was thought to be the ultimate solution as other treatment options were unsuitable or had failed to provide symptomatic relief; 5) absence of the following disorders: renal failure (creatinine >150

mmol/L), active pelvic infection, clotting disorders, allergy to contrast fluid, (suspected) uterine malignancy, submucosal fibroids protruding by >50% within the uterine cavity, or pedunculated abdominal fibroids; 6) no desire for future pregnancy.

Randomization was performed 1:1 to UAE or hysterectomy using a computer-based minimisation scheme ('balancing procedure'), stratified for study centre. Written informed consent was obtained in all patients. The study was approved by the Dutch Central Committee Involving Human Subjects (www.ccmo.nl) and by local ethic committees. The EMMY trial was registered at Clinicaltrials.gov, number NCT 00100191.

PRE-ASSESSMENT

All patients were first seen at the gynecology outpatient clinic, and after assessment of the inclusion and exclusion criteria, eligible patients were informed by the attending gynecologist about the EMMY trial. All eligible patients received standardized written information about the trial and were scheduled for a next appointment where they could consent to trial participation.

Menstruation characteristics were assessed by the gynecologist in all patients before randomization. All patients completed a questionnaire including the pictorial blood loss assessment chart (PBAC) [10]. Patients were asked to fill out the pictorial chart as perceived on a single average day of menstrual blood loss based on the last two menstruations. This score was then multiplied by the average number of menstruation days to estimate the average amount of menstrual blood loss. This is a slightly modified version of the original PBAC.

Bulk-related complaints were assessed: the sensation of pressure in the lower abdomen, nycturia, increased urinary frequency and urinary incontinence. Furthermore both menstrual related and non-menstrual related pain were assessed. A hemoglobin level was obtained from each patient. All patients underwent a pelvic ultrasound either transvaginally and/or abdominally before treatment. The largest fibroid was indicated as the dominant fibroid. The uterus and dominant fibroid were measured in three dimensions, i.e. longitudinal (D1), anterior-posterior (D2), and transverse (D3). Volumes were calculated using the formula (D1 $\times$ D2 $\times$ D3 $\times$ 0.5233)[11]. Location of the dominant fibroid and the total number of fibroids was recorded.

MR imaging was performed only in the UAE group using a standardized imaging protocol, using various 1.0 and 1.5 T MRI scanners, all equipped with a phased array body coil. Sagittal T_1-weighted TSE images were performed as well as T_2-weighted images in sagittal, axial and coronal planes with slice orientation perpendicular and parallel to the long axis of the uterine cavity. Uterine and dominant fibroid volumes, location of the dominant fibroid and the number of fibroids were recorded similar to ultrasound.

UTERINE ARTERY EMBOLIZATION

Embolization was performed as described previously [12]. All radiologists were experienced in intervention radiology, including various embolization techniques in general. The first 2 or 3 procedures were supervised by an interventional radiologist (JR) with ample experience in UAE (> 50 UAE procedures). UAE was performed under local or epidural/spinal anesthesia. Femoral artery access was obtained uni- or bilaterally using 4- or 5-French catheters or microcatheters. Embolization was standardized in all patients and was carried out using only polyvinyl alcohol particles (PVA, Contour, Boston Scientific, Beek, The Netherlands) with a size of 355-500 μm. In cases where an anastomosis with the ovarian artery was observed, 500-700 μm particles were used instead [13]. PVA was injected into each uterine artery until parenchyma filling of the fibroids had stopped (target embolization) or until the main uterine artery was blocked with stasis of contrast (selective embolization).

After the procedure women were admitted to the gynecology ward for further care.

The protocol did not allow re-embolization in case of technically or clinically failure of the UAE procedure and these patients were offered hysterectomy.

HYSTERECTOMY

The type of hysterectomy and the route of access were not standardized and left at the discretion of the attending gynecologist, in order to keep as close to daily practice as possible. The following procedures were allowed: abdominal hysterectomy, either by median or a pfannenstiel incision, vaginal hysterectomy, laparoscopically assisted vaginal hysterectomy and laparoscopic hysterectomy. Both supravaginal and total hysterectomies were allowed. After the procedure women were admitted to the gynecology ward for further care.

FOLLOW-UP

After treatment patients were prospectively followed for two years at the gynecology out-patient clinic, at 6 weeks, and 6, 12 and 24 months respectively. At each follow-up visit, menstrual characteristics (only in the UAE group), lower abdominal pain and bulk-related symptoms (i.e. the sensation of pressure in the lower abdomen, nycturia, increased urinary frequency and incontinence) were recorded. Changes in these three dimensions compared to baseline were assessed using the following scale: worse, no change, slight improvement, significant improvement, no complaints anymore. The PBAC was obtained by mailed questionnaires at all follow-up visits only in the UAE group. Blood work was repeated. In the UAE group an ultrasound examination was performed at each visit. At 6 months a MRI scan was performed. Any re-interventions were recorded in the case record form.

SAMPLE SIZE AND ENDPOINTS

Since UAE can never exceed the effectiveness of hysterectomy in reducing complaints of menorrhagia, we performed a non-inferiority trial under the assumption that UAE should be considered non-inferior to hysterectomy whenever menorrhagia resolved in at least 75% of patients, in whom consequently a hysterectomy could be avoided. The cut-off point of 75% (allowing a maximum of 25% ($\Delta = 0.25$) of UAE patients to be clinical failures after two years of follow-up) was based on the results of similar trials comparing various alternative treatment modalities for menorrhagia, which proved to avoid hysterectomy in 79%, 76%, 74% and 70% of cases [14-17].

To reject the null hypothesis that UAE and hysterectomy are not clinically equivalent, at least 2 x 60 (=120) analyzable patients had to be included. In this power calculation, we used the following assumptions: expected effectiveness of UAE = 0.875, as reported in cohort studies available at the design phase of this trial [18-21]; expected effectiveness of hysterectomy = 0.999; threshold value $\Delta = 0.25$; $\alpha = 0.05$ (one-sided); $1\text{-}\beta = 0.90$.

Secondary endpoints were additional interventions, i.e. apart from hysterectomy, changes in bulk-related complaints, pain and hemoglobin levels in both groups. In the UAE group changes in uterine and dominant fibroid volume until 2 years after the initial treatment were evaluated.

STATISTICAL ANALYSIS

All data entries were visually double checked by an independent second investigator. Analyses were done using SPSS statistical software (version 11.5.1).

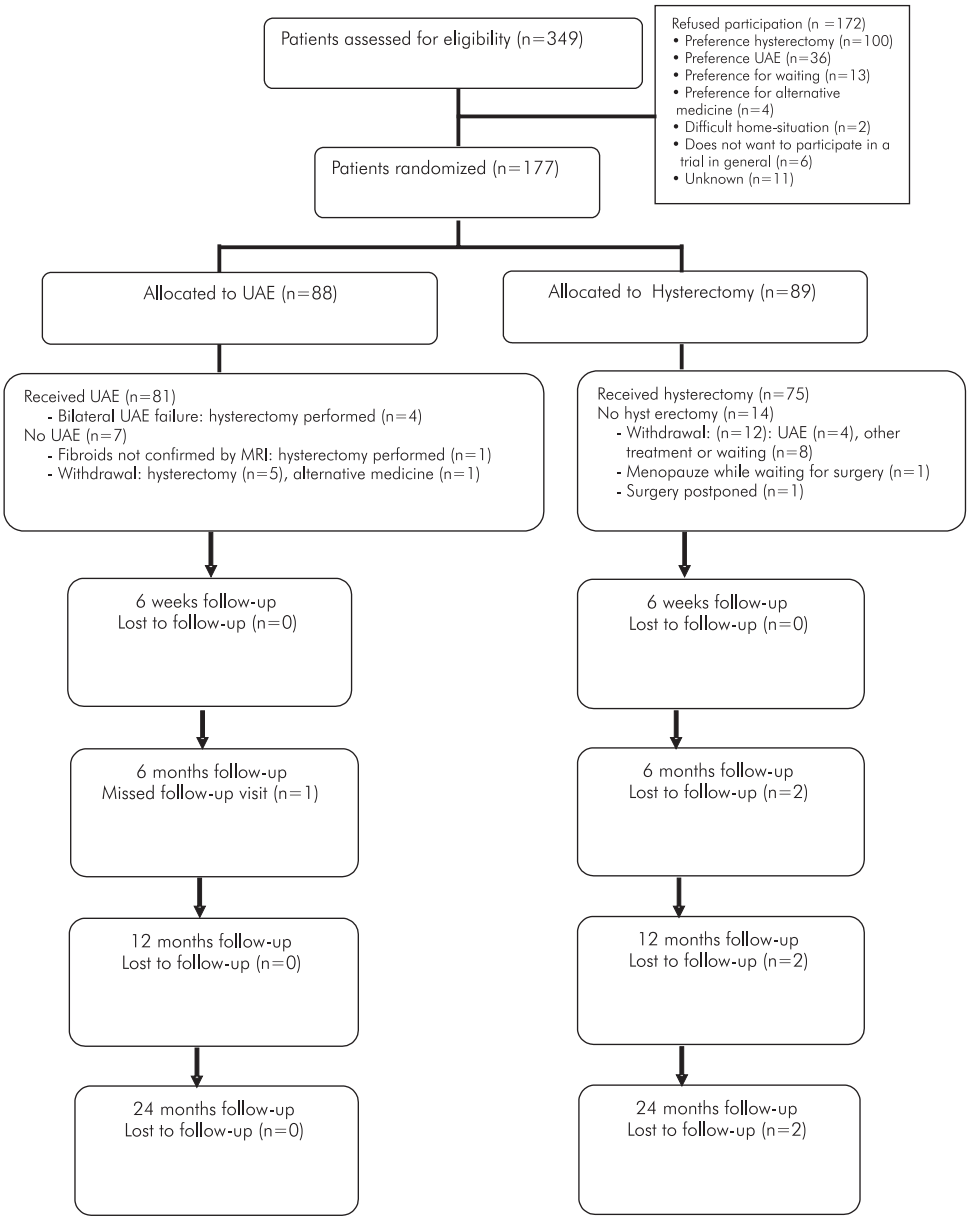
Differences in baseline characteristics were tested with multiple logistic regression analysis.

Study outcomes were analyzed according to original treatment assignment (intention to treat). Per-protocol analysis (i.e. excluding the failures in the UAE group) was performed for the hemoglobin level.

Differences in improvement in symptoms between groups were expressed in absolute numbers and % with 95% confidence interval (95%CI). Confidence intervals were calculated with SPSS or Statcalc (EpiInfo version 5). Differences in categorical data were compared with χ^2-tests or Fisher Exact tests if appropriate. Differences in numerical data were compared with Student's t-tests. Analyses for differences in bulk-related complaints and pain were only performed in patients who reported these complaints at baseline. Hemoglobin levels between groups over time were compared using a two-way ANOVA repeated measurement analysis. Predictors for failure (secondary hysterectomy) were tested using logistic regression analysis. In this analysis the following baseline characteristics were included for multiple regression analysis, whenever univariate analysis revealed p-values < 0.1: age (continuous), ethnicity (caucasian

as reference category), BMI (continuous), parous (yes/no), smoking (yes/no), co-morbidity (yes/no), previous surgical treatment (yes/no), previous hormonal treatment (yes/no), duration of menorrhagia symptoms (>/< 1 years), modified PBAC score (continuous), hemoglobine level (continuous), anemia (yes/no), radiologist's experience, for ultrasound and MRI: number of fibroids (continuous), uterine volume (continuous), dominant fibroid volume (continuous),

FIGURE 1. Trial profile



location of dominant fibroid (submucosal, subserosal, intramural, not classified), flow in dominant fibroid using ultrasound (hypovascular, isovascular or hypervascular) , T_2 signal intensity on MRI (hyperintens, isointens, hypointens, mixed), concomitant adenomyosis. A p-value of <0.05 was considered statistically significant.

RESULTS

PATIENTS

Patients were enrolled between March 2002 and February 2004. Twenty-eight of the thirty-four participating hospitals included patients. Of 349 eligible patients, 177 were randomized: 88 were allocated UAE and 89 hysterectomy (Figure 1). After randomization 7 patients in the UAE group and 14 patients in the hysterectomy group refused the allocated treatment. Patients who refused the assigned treatment were comparable to participants in terms of age, race, BMI, parity, symptoms and duration of symptoms (data not shown). At 24 months follow up 2 patients in the hysterectomy group and none in the UAE group were lost to follow up. Table 1 describes the baseline characteristics of our participants. Logistic regression analysis did not reveal any baseline characteristics to be predictive of treatment allocation, thus confirming successful randomization.

TABLE 1. Baseline and procedural characteristics

	UAE n=88 n (%)	Hysterectomy n=89 n (%)
BASELINE CHARACTERISTICS		
Age (years)		
Mean (SD)	44.6 (4.8)	45.4 (4.2)
Body Mass Index (weight (kg) / length $(m)^2$)		
Mean (SD)	26.7 (5.6)	25.4 (4.0)
Parity		
0	30 (34.1)	20 (22.5)
1/>1	58 (65.9)	69 (77.5)
Ethnicity		
White	54 (61.4)	57 (64.0)
Black	24 (27.3)	20 (22.5)
Other	10 (11.4)	12 (13.5)
Smoking status		
Current smoker	21 (23.9)	23 (25.8)
Former smoker	11 (12.5)	14 (15.7)
Non-smoker	56 (63.6)	52 (58.4)

TABLE 1. Continued

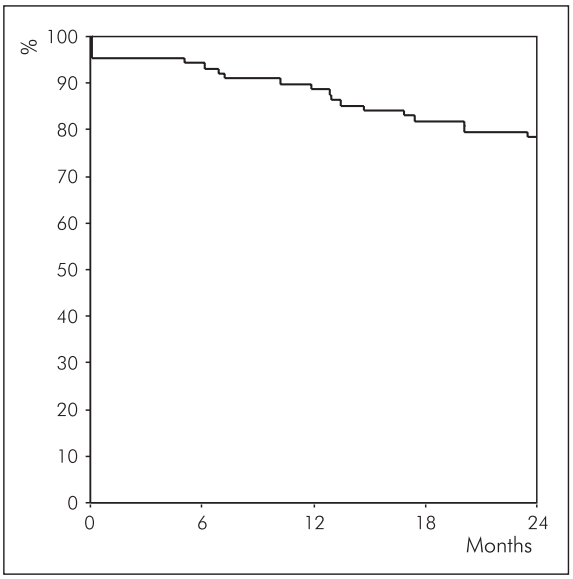
		UAE n=88 n (%)	Hysterectomy n=89 n (%)
Highest educational level *1			
Elementary school		3 (3.4)	6 (6.9)
Lower vocational, lower secondary school		29 (33.0)	32 (36.8)
Intermediate and higher vocational, higher secondary school		26 (29.5)	27 (31.0)
College/University		28 (31.8)	22 (25.3)
Other		2 (2.3)	0 (0)
Previous treatment			
None		11 (12.5)	15 (16.9)
Hormonal		59 (67.0)	59 (66.3)
Non-Steroidal-Anti-Inflammatory-Drugs /Tranexaminacid		45 (51.1)	41 (46.1)
Iron-supplement/blood transfusion		50 (56.8)	52 (58.4)
Surgical procedures *2		17 (19.3)	11 (12.4)
Myomectomy		13 (14.8)	13 (14.6)
Hysteroscopic endometrium resection		3 (3.4)	1(1.1)
Curettage		3 (3.4)	0 (0)
Symptoms			
Menorrhagia		88 (100)	89 (100)
Anemia		43 (48.9)	42 (47.2)
Lower abdominal pain		73 (82.9)	61 (68.5)
Bulk-related complaints		68 (77.3)	67 (75.3)
Duration of symptoms (months)			
Median (range)		24 (3-250)	24 (4-240)
Duration of menstruation (days)			
Total days (median, range)		7 (4-28)	8 (3-42)
Heavy days (median, range)		3 (1-28)	4 (1-21)
Modified PBAC			
Median (IQR)		850 (429-1483)	952 (475-1453)
Number of fibroids *3			
Median (range)		2 (1-20)	2 (1-9)
PROCEDURAL CHARACTERISTICS			
Type of UAE			
Target embolization	Left uterine artery	65	-
	Right uterine artery	59	-
Selective embolization	Left uterine artery	8	-
	Right uterine artery	12	-
Type of hysterectomy		(n=4)	
Abdominal hysterectomy		(2)	63
Vaginal hysterectomy		(1)	8
Vaginal hysterectomy with morcellator		(1)	1
LH with morcellator		-	2
LAVH		-	1
Cervix			
Conservation of cervix		(2)	22

Data were available for all or all but 1 patient, unless stated otherwise. Number of fibroids was calculated by ultrasound unless stated otherwise. *1 hysterectomy missing: 2; *2 The surgical treatments do not add up because some patients had several treatments; *3 UAE missing: 5, hysterectomy missing: 11. Logistic regression analysis did not reveal baseline characteristics that could predict randomization outcome.

TABLE 2. Re-interventions in UAE and hysterectomy group until 2 years after initial treatment

Primary intervention	Secondary intervention	Reason for intervention	Time since primary intervention (months)
UAE			
1	Abdominal hysterectomy	Bilateral failure UAE	<1
2	Abdominal hysterectomy	Bilateral failure UAE	<1
3-1	Abdominal hysterectomy	Bilateral failure UAE	<1
3-2	Laparoscopic reconstruction surgery	Incisional hernia	9
4	Vaginal hysterectomy with morcellation	Bilateral failure UAE	<1
5-1	Failed attempt to hysteroscopically remove fibroid under general anesthesia	Persistent abdominal pain/myoma nascens	1
5-2	Attempt to hysteroscopic fibroid resection: converted to vaginal hysterectomy	Return menorrhagia	20
6	Manual resection fibroid under general anesthesia	Discharge, fever and abdominal pain/ myoma nascens	2
7	Abdominal hysterectomy	Menorrhagia and persistent abdominal pain	5
8	Abdominal hysterectomy	Menorrhagia	6
9	Abdominal hysterectomy	Menorrhagia, persistent pain, bulk complaints	7
10	Abdominal hysterectomy	Menorrhagia	7
11	Abdominal hysterectomy	Persistent abdominal pain and irregular menstruation	10
12	Vaginal hysterectomy	Menorrhagia, persistent pain and dyspareunia	12
13-1	Diagnostic hysteroscopy with curettage	Post menstrual blood loss	12
13-2	Abdominal hysterectomy	Irregular cycle, pain and bulk complaints	13
14	Abdominal hysterectomy	Menorrhagia and bulk complaints	13
15	Abdominal hysterectomy	Return menorrhagia	13
16	Laparoscopic assisted vaginal hysterectomy	Menorrhagia	15
17	Abdominal hysterectomy	Menorrhagia	17
18	Vaginal hysterectomy	Menorrhagia	17
19	Abdominal hysterectomy	Menorrhagia	20
20	Abdominal hysterectomy	Menorrhagia	24
Hysterectomy			
1-1	Adhesiolysis via laparotomy	Persistent abdominal pain	4
1-2	Bilateral adnex-extirpation	Persistent abdominal pain	11
2	Fistula repair using Latzko technique	Vesico-vaginal fistula	7
3	Reconstruction surgery	Incisional hernia	9
4	Adhesiolysis and cystectomy via laparotomy	Persistent abdominal pain	23
5	Diagnostic laparoscopy	Persistent abdominal pain	24

FIGURE 2. Kaplan-Meier curve for preservation of the uterus after UAE



PROCEDURES

Bilateral failure of the procedure occurred in 4 patients (4.9%) who subsequently underwent a hysterectomy. Ten patients had a unilateral UAE (12.3%). In most cases (86.1%) target embolization was carried out. In the hysterectomy group, all operations were technically successful. Most hysterectomies were performed transabdominally (84.0%).

MAIN OUTCOMES

Re-interventions during the 2-year follow-up period are shown in Table 2. At 24 months, 19/81 hysterectomies (23.5%; 95%CI: 14.8-34.2; p=0.43) had been performed in the UAE group. Thus, the null hypothesis cannot be rejected (p=0.43). These hysterectomies were evenly distributed over time (Figure 2). Exclusion of bilateral technically failed UAE procedures, resulted in 15/77 (19.5%) hysterectomies in women undergoing successful UAE. All hysterectomies but one were performed because of persistence or relapse of menorrhagia. In one patient menorrhagia resolved, but pain and bulk-related complaints worsened, and necessitated a secondary hysterectomy. The multiple regression analysis on failure revealed that only parous was associated with a higher risk for failure (ß=1.39; 95%CI: 1.33-12.22; p=0.014).

Histopathology confirmed fibroids in all but one patients: in one case, only adenomyosis was found. Three patients showed additional abnormalities apart from fibroids: adenomyosis in one, a tubo-ovarian abscess in another (this patient had a bilaterally failed UAE attempt) while in a third patient, subsequently endometrial carcinoma 1c grade 2 was diagnosed after

persistent abnormal uterine bleeding. After undergoing hysterectomy, additional radiotherapy was carried out, and no evidence of recurrence has been noted after 18 months.

Re-interventions other than hysterectomies in the UAE group were: two hysteroscopic procedures for removal of necrotic fibroid tissue, one incisional hernia repair (after secondary hysterectomy) and one diagnostic hysteroscopy for post-menopausal bleeding.

In the hysterectomy group 6 (8.0%) additional re-interventions were performed: one incisional hernia repair, one Latzko-repair of a vesico-vaginal fistula, and four procedures (three laparoscopies and one laparotomy) for persistent abdominal pain after primary treatment. These four patients continued to have persistent abdominal pain at 24 months of follow-up.

Table 3 describes bleeding characteristics of the UAE group. The results include those patients undergoing subsequent hysterectomies after failed UAE. Overall, on average all

TABLE 3. Menstruation changes until 2 years after UAE (intention to treat). Hysterectomy patients are not included since they are symptom free by definition

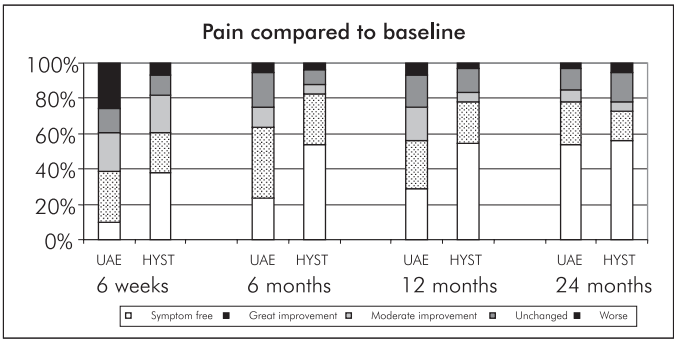
Menorrhagia*[1]	Baseline n (%) n=88	6 weeks n (%) n=81
Symptom free	NA	16 (19.8)
Great improvement	NA	24 (29.6)
Moderate improvement	NA	20 (24.7)
Unchanged	NA	16 (19.8)
Worse	NA	5 (6.2)
Menstruation		
Duration of menstruation (median,range) (days)	7 (4-28)	6 (0-40)
Duration of heavy menstruation (median, range) (days)	3 (1-28)	2 (0-14)
Presence of bloodclots (%)	95.40%	46.90%
No. of pads used on heaviest bleeding day (median, range)	9.5 (3-24)	6 (0-28)
PBAC (median, interquartiles)	850 (429-1483)	323 (70-790)
Additional treatment for menorrhagia		
Iron-supplement	NA	7
Tranexamine acid	NA	2
Lynestrenol	NA	-
Oral anticonceptive	NA	1
Levonorgestrel intra-uterine device	NA	-
GnRH-analogues	NA	-
Total, in n patients (%)	NA	10, 10 (12%)
Amenorrhoe		
Due to hysterectomy	NA	4
Due to FSH > 30 E/l	NA	3
Due to pregnancy	NA	0
Due to medication*[4]	NA	1
No menstruation yet since UAE	NA	4
Cause unknown	NA	0
Total n (%)	NA	12 (15%)

menstruation parameters decreased over time. With regard to menorrhagia, at 24 months 50/81 patients were symptom free, whereas 3/81 patients described their menorrhagia as being unchanged compared to baseline.

At 24 months 16 (20.0%) UAE patients had 18 additional treatments, mostly iron supplements. In this subgroup, 3 women subsequently underwent hysterectomy. Excluding those patients undergoing secondary hysterectomy, there were 15 additional medical treatments in 13 (18.5%) UAE patients. In the hysterectomy group iron supplement therapy was also prescribed in 11 patients (14.7%) within the first 6 weeks after the procedure. Until 6 months this was continued for 1 patient (1.3%). In the hysterectomy group 3 patients (4.0%) had minimal cyclic vaginal blood loss after undergoing supravaginal hysterectomy.

	6 months n (%) n=80	12 months n (%) n=81	24 months n (%) n=81
	24 (30.0)	35 (43.2)	50 (61.7)
	31 (38.8)	23 (28.4)	22 (27.2)
	18 (22.5)	14 (17.3)	6 (7.4)
	4 (5.0)	6 (7.4)	3 (3.7)
	3 (3.8)	3 (3.7)	0 (0.0)
	5 (0-14)	5 (0-14)	4 (0-21)
	2 (0-7)	1 (0-10)	0 (0-6)
	42.00%	38.30%	21.00%
	6 (0-48)	5 (0-20)	4 (0-14)
	127 (51-396)	82 (0-386)	45 (0-166)
	6	8	11*2
	3	3	2
	1	1	1
	3	2	1
	2	-	1
	-	1	2*3
	15, 14 (18%)	15, 12 (15%)	18, 16 (20%)
	5	9	19
	4	7	8
	0	1	0
	0	2	2
	0	0	0
	2	0	1
	11 (14%)	19 (23%)	30 (37%)

*1 in one patient after secondary hysterectomy; *2 Either continuous oral anticonceptive use, levonorgestrel intra-uterine device, or GnRH analogues; *3: These 2 patients subsequently had a hysterectomy; *4 when a secondary hysterectomy had occurred this patient was 'symptom free'; NA: not applicable



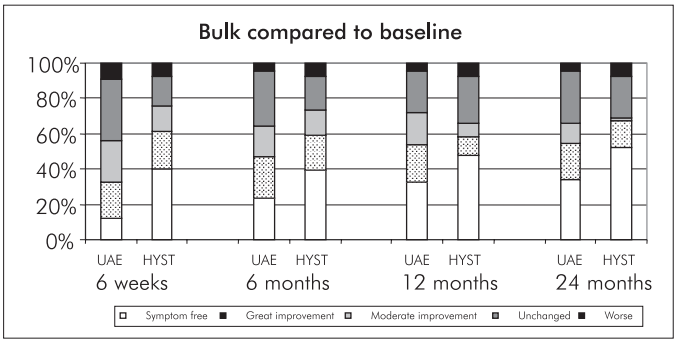


FIGURE 3. Pain and bulk-complaints compared to baseline using χ^2-test or Fisher Exact test

TABLE 4. Volume change of the uterus and dominant fibroid using ultrasound and MRI until 2 years after UAE

	Baseline	6 weeks	6 months
ULTRASOUND			
Uterine volume (cm^3)	n=87	n=69	n=66
Mean (SD)	471.9 (450)	268.8 (209)	235.3 (204)
Median (range)	321.2 (31-3005)	218.6 (31-977)	162.5 (28-1315)
% reduction from baseline (95%CI)	NA	20.9% (7.0-34.9)	30.9% (17.3-44.5)
p-value	NA	<0.0001	<0.0001
Dominant fibroid volume (cm^3)	n=87	n=72	n=73
Mean (SD)	121.5 (150)	70.5 (105)	54.4 (95)
Median (range)	58.6 (1-673)	29.3 (0-402)	18.8 (0-483)
% reduction from baseline	NA	14.8% (-21.1-50.8)	42.1% (25.3-58.9)
p-value	NA	0.0003	<0.0001
MRI			
Uterine volume (cm^3)	n=83	NA	n=73
Mean (SD)	557.3 (635.4)	NA	336 (579.7)
Median (range)	378.8 (46.2-3970.0)	NA	197.1 (20.7-3725.3)
% reduction from baseline (95%CI)	NA	NA	43.5% (38.0-49.1)
p-value	NA	NA	<0.0001
Dominant fibroid volume (cm^3)	n=83	NA	n=73
Mean (SD)	174.6 (232.4)	NA	84.2 (165.8)
Median (range)	70 (2.3-1078.0)	NA	19.9 (0-983.8)
% reduction from baseline	NA	NA	48.4% (21.9-74.8)
p-value	NA	NA	<0.0001

NA: not applicable

At 24 months 30/81 patients showed amenorrhoea due to hysterectomy (23.5%), a high FSH value (9.9%), medication (2.5%) or unknown causes (1.2%). After UAE 1 unplanned pregnancy occurred in a 39 year old multipara. At 39+5 weeks she delivered a healthy child after secondary caesarean section for fetal distress (Apgarscores: 3/7/9; birth weight: 2780 gram, ~ 3rd percentile).

Figure 3 describes lower abdominal pain and bulk complaints compared to baseline values at the various follow up visits for patients who had these complaints at baseline (UAE group: n=73/81 (pain) and 68/81 (bulk-related); hysterectomy group: n=61/75 (pain) and 67/75 (bulk-related). At 24 months follow up 84.9% of UAE patients reported at least moderate improvement of pain, compared to 78.0% of hysterectomy patients (p=0.30). For bulk-related complaints this was 66.2% versus 69.2% (p=0.71). Analysis of trend for the 5 categories of change compared to baseline for pain, favored hysterectomy at all time points, except for 24 months where no significant difference between both groups was observed (6 weeks: p=0.001; 6 months: p=0.007; 12 months: p=0.03; 24 months: p=0.88). Of the remaining patients without pain at baseline, only 1 patient in the hysterectomy group reported worsening of symptoms.

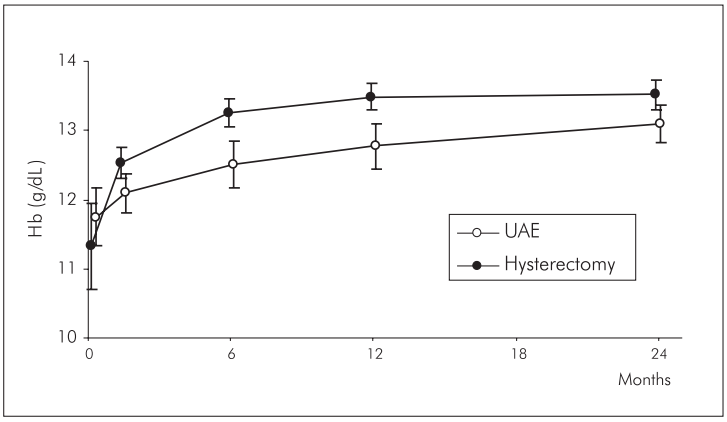
For bulk-complaints the only significant difference was found at 6 weeks favoring the hysterectomy group (6 weeks: p=0.002; 6 months: p=0.24; 12 months: p=0.12; 24 months: p=0.052). Patients without bulk complaints at baseline reported no worsening of symptoms at 24 months of follow up.

12 months	24 months
n=62	n=62
201.2 (198)	170.2 (135)
134.8 (16-1292)	136.1 (18-754)
44.3% (32.5-56.2)	48.2% (39.2-57.1)
<0.0001	<0.0001
n=66	n=62
41.6 (78)	40.1 (87)
11.4 (0-490)	6.1 (0-478)
54.5% (36.1-72.8)	60.5% (46.1-75.0)
<0.0001	0.0001
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA
NA	NA

Volume reduction of both fibroids and uterus in the UAE group assessed by ultrasound and MRI are listed in Table 4. Uterine and fibroid volume reduction was highly significant for all time points, both for ultrasound and for MRI (p<0.001 at all time points). At 24 months uterine volumes decreased by 48.2% (95%CI: 39.2-57.1%) compared to baseline. For dominant fibroid volume this was 60.5% (95%CI: 46.1-75.0%).

Figure 4 depicts average hemoglobin levels from baseline until 2 years of follow up. In both groups hemoglobin levels increased significantly compared to baseline (at 24 months: UAE: +1.37 g/dL, 95%CI: 0.903-1.84, p<0.0001;

FIGURE 4. Hemoglobin levels from baseline until 24 months follow-up



hysterectomy: +2.03 g/dL, 95%CI: 1.44-2.61, p<0.0001). Increase in hemoglobin was significantly higher for hysterectomy patients (p=0.037). The per-protocol analysis of changes in hemoglobin levels over time showed similar results.

DISCUSSION

This is a large, long term follow-up, randomized trial that compares UAE 1:1 to hysterectomy in the treatment of menorrhagia caused by uterine fibroids.

We conclude that UAE is a good alternative to hysterectomy: the failure rate of UAE, defined as the necessity to perform a hysterectomy in the first two years after embolization, stayed within the preset failure rate maximum of 25%: when an actual UAE was attempted (in 81/88 patients) 23.5% (19/81) had had a secondary hysterectomy during the 24 months follow up period. Nevertheless, the 76.5% success rate is much lower than results from earlier uncontrolled series, which reported subsequent hysterectomy rates between 1.5% and 4.5% depending on the duration of follow up. This underlines the importance of randomized controlled trials [2;4-6]. The only pre-consent randomized trial comparing UAE with hysterectomy found a failure rate of 14% (persistence of heavy menstrual bleeding), while another 7.5% (3/40) UAE patients underwent hysterectomy after completing 24 months of follow up [22]. Another cohort study reporting on 5 years follow-up, reported 19.8% re-interventions (hysterectomy/myomectomy/re-embolization), which comes close to our findings [23]. Although our success rate was lower than reported in the literature, volume reductions (24 months: uterus: 48.2%, dominant fibroid: 60.5%), in the UAE group were comparable to the literature indicating adequate embolization [5;6].

The lower effectiveness of UAE in our trial can be explained as follows. Firstly, patients participating in our study had severe bleeding problems, as illustrated by the impressive symptomatology and previous medical and surgical history (Table 1). Included patients were all candidates for undergoing hysterectomy, hence they represented the severe end of the clinical spectrum. One might speculate that UAE is likely to perform better in patient with less severe complaints, which indeed applies to earlier published reports where the majority of included patients were self-selected cases. Secondly, we found a higher technical failure rate compared to the literature: bilateral failure occurred in 4 patients (4.9%). In these patients vessels could not be embolized due to pure technical failure or were found to be absent [9]. Thirdly, re-embolizations were not allowed in our study and recurrence was seen as a definite failure. In many published reports, re-embolizations are allowed and this could have increased UAE success rates. Finally, in contrast to other reports [6;23;24], our results do not derive from a single high volume centre which may perform better. We do believe that instead of being a flaw, arguably, this enhances the generalizability of our findings since many clinical settings are very similar to those described in this study. We were unable to identify factors that could predict failure of UAE. Only parity was significantly associated with failure. We cannot explain this easily. Apparently, an embolization performed on a uterus that had carried a pregnancy was less probable to succeed. However, other factors like experience of the radiologist, uterine volumes and other MRI parameters were not associated with an increased failure risk.

Some other points deserve further discussion.

We did not apply a strict definition of menorrhagia as an inclusion criterion and used pictorial charts only for the comparison of menstrual bleeding before and after UAE. We decided to do so, although it is well known that the subjective assessment of menstrual blood loss is often inadequate [25]. Also in daily practice the decision to perform a hysterectomy is not based on pictorial charts or other objective measurements of menstrual blood loss, but rather on the patient's subjective appreciation combined with the overall clinical symptomatology.

Furthermore, although a hysterectomy could be avoided in 76.5% of cases, an additional three patients (3.7%) reported no improvement of their menstrual bleeding pattern compared to baseline at 24 months follow-up. Whether these will result in subsequent hysterectomies remains to be awaited. Therefore these cases were not considered as clinical failures in the present analysis. The fact that UAE may not result in complete cessation of menorrhagia, while additional medication may be required (in 13/81 patients at 24 months), illustrates that hysterectomy still provides the best guarantee for immediate and complete relief of menstrual problems.

Additionally, we would like to clarify why so called bulk related complaints were still present after hysterectomy in many cases. As already stated earlier, bulk related complaints consisted of various symptoms besides the sensation of pressure also of increased urinary frequency, nycturia and urinary incontinence. The majority of these complaints can also develop or worsen after hysterectomy.

Finally, although UAE prevented a secondary hysterectomy in >75% of cases, thereby proving itself to be a valuable alternative to hysterectomy, other outcomes should also be considered when deciding between the treatments. A previous publication showed neither significant differences in major complication rates (4.9% (UAE) vs. 2.7% (hysterectomy) of cases; p=0.68), nor differences in overall minor complication rates (64.2% (UAE) vs. 56.0% (hysterectomy); p=0.38) [9]. Although UAE patients were readmitted more often following treatment (11.1% vs. 0%; p=0.003), hospital stay was significantly shorter in UAE patients (mean: 2.5 vs. 5.1 days, p<0.001). Moreover, UAE patients recovered more quickly than hysterectomy patients, while pain was less severe after UAE during the first 24 hours [7]. These findings demonstrate that UAE is a serious alternative treatment, with several clear advantages over hysterectomy.

In conclusion, UAE is a valuable treatment for symptomatic uterine fibroids, avoiding hysterectomy in 76.5% of cases (intention to treat) or 80.5% after technically successful UAE, at 2 years follow-up. UAE has comparable results to hysterectomy concerning pain and bulk symptoms. Nevertheless when patients seek for absolute certainty on the cessation of bleeding problems, a hysterectomy still remains the treatment of choice.

ACKNOWLEDGEMENTS

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HUMAN REPRODUCTION
IN PRESS

7

LOSS OF OVARIAN RESERVE AFTER UTERINE ARTERY EMBOLIZATION: A RANDOMIZED COMPARISON WITH HYSTERECTOMY

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ABSTRACT

Background

Uterine Artery Embolization (UAE) is becoming increasingly popular as a treatment for symptomatic uterine fibroids. Ovarian failure as a complication of UAE has raised concerns about this new treatment modality.

Methods

We investigated the occurrence of ovarian reserve reduction in a randomized trial comparing UAE and hysterectomy by measuring follicle stimulating hormone (FSH), anti müllerian hormone (AMH) and menopausal symptoms. Pre-menopausal women with menorrhagia due to uterine fibroids were randomized (1:1) between UAE and hysterectomy. At baseline and follow-up visits FSH was measured and self-report menopausal symptom questionnaires were administered. In a subset of 63 patients AMH was measured as well. Follow-up AMH levels were compared to baseline and to the expected decrease due to ovarian ageing during the observational period.

Results

177 patients were randomized to UAE (n=88) and hysterectomy (n=89). FSH increased significantly compared to baseline in both groups after 24 months follow up (within group analysis: UAE: +12.1; 95%CI: 6.7-17.4; p=0.001; hysterectomy: +16.3; 95%CI: 9.8-22.7; p<0.0001). No differences between the groups were found (p=0.32). At 24 months after treatment the number of patients with FSH levels > 40 IU/L was 14/80 in the UAE group and 17/73 in the hysterectomy group (RR= 0.75; 95%CI: 0.40-1.41; p=0.37). Multiple regression analysis revealed that age > 45 years was predictive for the development of FSH levels >40 IU/L. At 24 months no significant differences in menopausal symptoms were observed between the groups.

AMH was measured in 63 patients (UAE: n=30; hysterectomy: n=33). After treatment AMH levels remained significantly decreased during the entire follow up period only in the UAE group compared to the expected AMH decrease due to ageing. No differences were observed between the groups.

Conclusion

This study shows that both UAE and hysterectomy affect ovarian reserve. This results in older women becoming menopausal after the intervention. Therefore, the application of UAE in women who still wish to conceive should only be considered after appropriate counseling.

INTRODUCTION

Since its introduction in 1995 uterine artery embolization (UAE) has become increasingly popular for the treatment of fibroid-related menorrhagia [1]. UAE has been proposed by some enthusiasts to replace hysterectomy altogether as a final solution for fibroid disease in selected patients. Safety and efficacy have been evaluated in several large case-series [2-5], but well designed randomized trials are lacking. Therefore, we initiated the randomized EMMY (EMbolization versus hysterectoMY) trial. Some short term and long term results of the EMMY trial have been published earlier [6-9].

Reduction of ovarian reserve after hysterectomy leading to (early) menopause has been described [10-14]. Since early menopause is associated with an increased risk for osteoporosis and cardiovascular disease [15-17], UAE might provide a benefit. However, also after UAE the onset of menopause has been described [18-21]. The true incidence of persistent ovarian failure after UAE is unknown but has been estimated to be < 2% [22]. No randomized controlled trials have focused on this subject. Permanent ovarian failure can be demonstrated by increased FSH and LH levels, increased menopausal symptoms and decreased oestradiol levels, which all occur typically after the onset of menopause [23].

To test the extent of ovarian reserve reduction (i.e. loss of oocytes) FSH, LH, oestradiol and menopausal symptoms are of no use, since they only change or occur after the actual onset of the menopausal transition [23;24]. Ovarian reserve reduction can better be tested by measuring Anti-Müllerian-Hormone (AMH). AMH in women reaches its highest level after puberty [25] and gradually decrease over time in normo-ovulatory women [26]. Furthermore AMH is cycle independent [27;28]. AMH has been acknowledged as being a reliable marker of ovarian reserve, especially in relation to the quantity of remaining follicles in the ovaries [29;30]. To the best of our knowledge, relative damage has not been tested after both hysterectomy and UAE.

This report focuses on the occurrence of ovarian reserve reduction after UAE in comparison to hysterectomy as determined by clinical (i.e. menopausal symptoms) and hormonal markers (i.e. FSH, LH, oestradiol and AMH).

METHODS

STUDY DESIGN

The EMMY (EMbolization versus hysterectoMY) study is a multi-centre, randomized controlled trial, conducted in the Netherlands. A detailed description of the study has been provided earlier and will be discussed here only briefly [6].

Patients were included when their predominant complaint was menorrhagia, they had uterine fibroids and were to be scheduled for hysterectomy. Patients who desired future pregnancy were excluded. After written informed consent had been obtained, computer-based randomization was carried out, assigning patients 1:1 to either UAE or hysterectomy.

The study was approved by the Central Committee Involving Human Subjects (www.ccmo.nl) and by the local ethics committees of all participating hospitals.

PROCEDURES

Uterine artery embolization

UAE was performed by an interventional radiologist. For UAE polyvinyl alcohol particles (PVA, Contour, Boston Scientific, Beek, The Netherlands) with a size of 355-500 μm were used. Only if an anastomosis with the ovarian artery was observed particles with a size of 500-700 μm were used to prevent migration of particles into the ovarian artery. PVA was injected into each uterine artery until there was no parenchyma filling of the fibroids anymore (target embolization) or until the main uterine artery was blocked and there was stasis of contrast (selective embolization). No selective embolization of ovarian arteries was carried out, because of the assumed high risk for ovarian damage. In case of extensive collaterals of the uterine artery to the cervix and vaginal wall, the procedure was stopped.

Hysterectomy

The type of hysterectomy and the route of access were left at the discretion of the attending gynecologist. We did not establish consensus guidelines for concomitant adnexal surgery. If adnexa were removed, note was made.

ENDPOINTS OF THE STUDY

To assess the impact of both treatments on the menopausal transition FSH, LH and oestradiol were measured in both groups at baseline and at 6 weeks and 6, 12 and 24 months follow up. Also menopausal symptoms were assessed at these time points, with an additional questionnaire at 18 months follow up.

Impact of treatments on ovarian reserve was tested by measuring AMH at baseline and 1 day, 6 weeks and 6, 12, 24 months after treatment. AMH was measured in a subset of patients for logistic reasons. These patients were recruited in the four hospitals (Academic Medical Centre, Amsterdam; Onze Lieve Vrouwe Gasthuis, Amsterdam; Universitary Medical Centre, Utrecht; Rijnstate Hospital, Arnhem) that were expected to contribute the largest number of patients to the trial and that could reliably store the samples before collecting them for analysis in a central laboratory.

Comparisons were made between the groups at all time points and within the groups compared to baseline.

BLOOD SAMPLING AND LABORATORY ASSAYS

FSH, LH and oestradiol were preferably taken on the third day of the menstrual cycle.

All blood samples were assayed for levels of FSH, LH and oestradiol using each hospital laboratory's own assay.

AMH blood samples were allowed to clot, centrifuged, serum collected, frozen at -20 ^{0}C within 3 hours and stored until assayed in a central laboratory. All samples used for serum AMH measurements were analyzed simultaneously (Laboratory for Internal Medicine, Erasmus Medical Centre) using an enzyme-immunometric assay (DSL Webster, TX, USA). Inter- and intra-assay coefficients of variation were below 5% at the level of 3 microgram/l, and below 11% at the level of 13 microgram/l. The detection limit of the assay was 0.026 microgram/l. Repeated freezing and thawing of the samples or storage at 37 °C for 1 hour did not significantly affect results. A comparison of this assay with the ultrasensitive version of the assay method provided by Immunotech-Coulter (Marseilles, France) in 82 samples with AMH concentrations between 0 and 15 microgram/l yielded a correlation coefficient of 0.85. The formula of the regression line was AMH (DSL) = 0.495*AMH(ic)-0.03. In order to keep results comparable with earlier published data, we multiplied all results by a factor 2.0 [29-31].

QUESTIONNAIRES ON MENOPAUSAL TRANSITION STATUS

Standardized questionnaires (Table 1) were used to measure menopausal symptoms: the Kupperman score [32], the Kupperman score as modified by Wiklund et al.[33] and a score developed by Oldenhave et al. yielding 3 dimensions: vasomotor complaints, atypical symptoms and vaginal dryness [34].

This resulted in scores ranging from 0-51 (original and modified Kupperman), 0-6 (vasomotor symptoms Oldenhave) and 0-63 (atypical symptoms Oldenhave). The Oldenhave vaginal dryness score reflects the weight of the individual score yielding a score ranging from 0 to 3. For all instruments higher scores represented more menopausal symptoms.

TABLE 1. Menopausal questionnaires

KUPPERMAN (0-51)	WIKLUND (0-51)	OLDENHAVE
vasomotor symptoms (x 4)	hot flashes (x 4)	Vasomotor complaints (0-6)
paraesthesia (x 2)	sweating (x 2)	flushes
insomnia (x 2)	sleep disturbance (x 2)	sweating
nervousness (x 2)	nervousness (x 2)	Atypical symptoms (0-63)
melancholia	depression	tenseness
vertigo	vertigo	palpitations
weakness/fatigue	fatigue	irritability
arthralgia/myalgia	arthralgia	pins and needles
headaches	headache	restless legs
palpitations	tachycardia	dizziness
formication*[1]	vaginal dryness	tiredness
		tiredness on waking
		depression
		forgetfulness
		lack of energy
		shortness of breath
		muscle or joint pain
		lack of self-confidence
		insomnia
		headache
		migraine
		burning micturition
		itching labia
		vaginal discharge
		urine loss
		Vaginal dryness (0-3)
		vaginal dryness

Question:
In the last month, did you experience.....

Answering options + weights:
absent = 0
slight = 1
moderate = 2
severe = 3

Scoring:
The sum of weights (sometimes multiplied by a factor indicated by (x..) yields the score.

*[1] the sensation of crawling ants under the skin

At the outpatient clinic visits (6 weeks and 6, 12, 24 months after treatment) UAE patients were asked if and when menstrual periods had resumed.

STATISTICAL ANALYSIS

Outcomes were analyzed according to the intention to treat principle unless stated otherwise. A p-value <0.05 was considered statistically significant. Plots were constructed for average values of FSH, LH, oestradiol, AMH and menopausal scores, using all available data at baseline, 6 weeks and at 6 months intervals after treatment (until 24 months). Missing values for laboratory results were not imputed. Both a within group and a between group analysis was performed for all outcome parameters. For parametric data a Student's t-test was performed, while for non-parametric data a Mann-Whitney-U or a Wilcoxon test was used. Change from baseline was calculated for all visits after treatment. Differences between the groups were calculated by analyzing change from baseline at 6 weeks and 6, 12, 24 months. Longitudinal differences between groups were evaluated with repeated

measurements analyzes for all longitudinally available data (i.e. both for hormones and menopausal questionnaires).

FSH values were categorized for each outpatient visit (<10, 10-20, 20-30, 30-40 and >40 IU/l). Logistic regression analysis was performed to assess the risk of the occurrence of menopause. Since menopausal status cannot be determined by absence of menstrual flow in hysterectomy patients, we used FSH levels in excess of 40 IU/L at 24 months follow up to assess menopause [23]. The normal mid-follicular FSH peak does not reach these levels, and therefore this cut-off value was assumed to indicate persistent ovarian arrest. The following co-variables were included in the logistic regression, whenever univariate analysis revealed p-values < 0.1: intended treatment (UAE/hysterectomy), age at baseline (>/< 45), ethnicity (caucasian, black or other), BMI (continuous), uterus volume (continuous), parity (parous/non-parous), smoking (yes/no), comorbidity (yes/no), previous surgical treatment (yes/no). This analysis was repeated for both groups (UAE/hysterectomy) separately as well. In the hysterectomy group the following variables were added: type of hysterectomy (abdominal/not abdominal) and duration of hysterectomy (continuous); in the UAE group the following variables were added: unilateral selective UAE (yes/no), bilateral selective UAE (yes/no), number of required vials of PVA (continuous), presence of anastomosing vessels between uterine and ovarian arteries as detected at angiography, either unilateral (yes/no) or bilateral (yes/no); secondary hysterectomy after UAE (yes/no).

The natural decrease of AMH was calculated according to an earlier report [31]. Follow up values of AMH measurements were compared to both baseline AMH values and the expected calculated AMH values. For AMH a per-protocol analysis was performed to assess the exact impact of UAE on ovarian reserve: whenever a secondary hysterectomy was performed in the UAE group the subsequent AMH-values were excluded from further analysis.

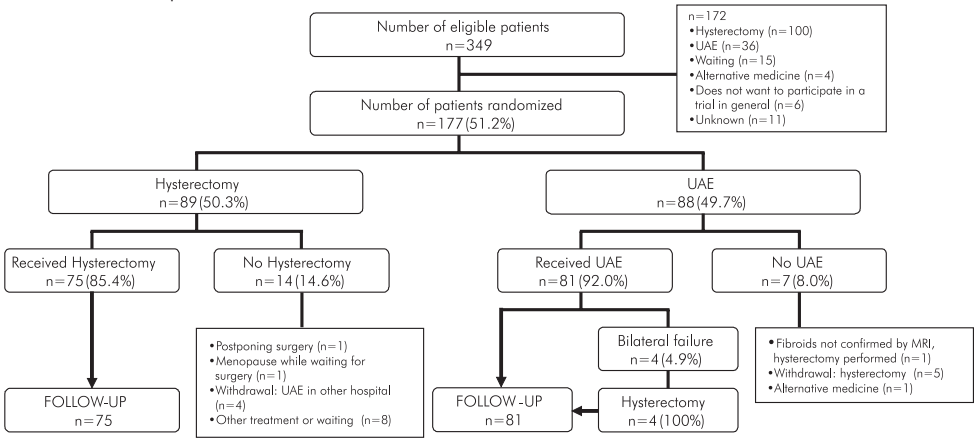
Subtle ovarian reserve reduction was explored by performing linear regression analysis with the change of AMH-level (24 months AMH-level minus baseline AMH-level) as the dependent variable, with the same co-variables and the same procedure as the logistic regression analysis described above. For the questionnaires, the average individual score was used when only 1 question was missing. In case of >1 question missing or when only the question on 'hot flashes' was missing, the whole score was excluded from analysis.

TABLE 2. Baseline characteristics

		UAE (n=88) n (%)	Hysterectomy (n=89) n (%)
Age (years)			
Mean (SD)		44.6 (4.8)	45.4 (4.2)
Body Mass Index (BMI) (Weight (kg) / length $(m)^2$)			
Mean (SD)		26.7 (5.6)	25.4 (4.0)
Parity			
0		30 (34.1)	20 (22.5)
≥ 1		58 (65.9)	69 (77.5)
Race			
Black		24 (27.3)	20 (22.5)
White		54 (61.4)	57 (64.0)
Other		10 (11.4)	12 (13.5)
Comorbid disease*[1]		24 (27.3)	22 (24.7)
Smoking status			
Current smoker		21 (23.9)	23 (25.8)
Former smoker		11 (12.5)	14 (15.7)
Non-smoker		56 (63.6)	52 (58.4)
Number of fibroids*[2]			
Median (range)		2 (1-20)	2 (1-9)
Uterine volume (cm^3)*[2]			
Median (range)		321 (31-3005)	313 (58-3617)
Fibroid volume (dominant fibroid, cm^3)*[2]			
Median (range)		59 (1-673)	87 (4-1641)
Type of UAE			
Target embolisation	Left uterine artery	65	-
	Right uterine artery	59	-
Selective embolisation	Left uterine artery	8	-
	Right uterine artery	12	-
Type of hysterectomy			
Abdominal hysterectomy		-	63
Vaginal hysterectomy		-	8
Vaginal hysterectomy with morcellator		-	1
LH with morcellator		-	2
LAVH		-	1
Uterine-ovarian artery anastomosis		15*[3]	Unknown
Other procedures			
Salpingo-oophorectomy			
Unilateral		-	2
Bilateral		-	1

*[1] At least one of the following: hypertension; diabetes; asthma; systemic disease; *[2] Ultrasound data; *[3] In 13 patients unilaterally, in 1 patient bilaterally

FIGURE 1. Trial profile



RESULTS

PATIENTS

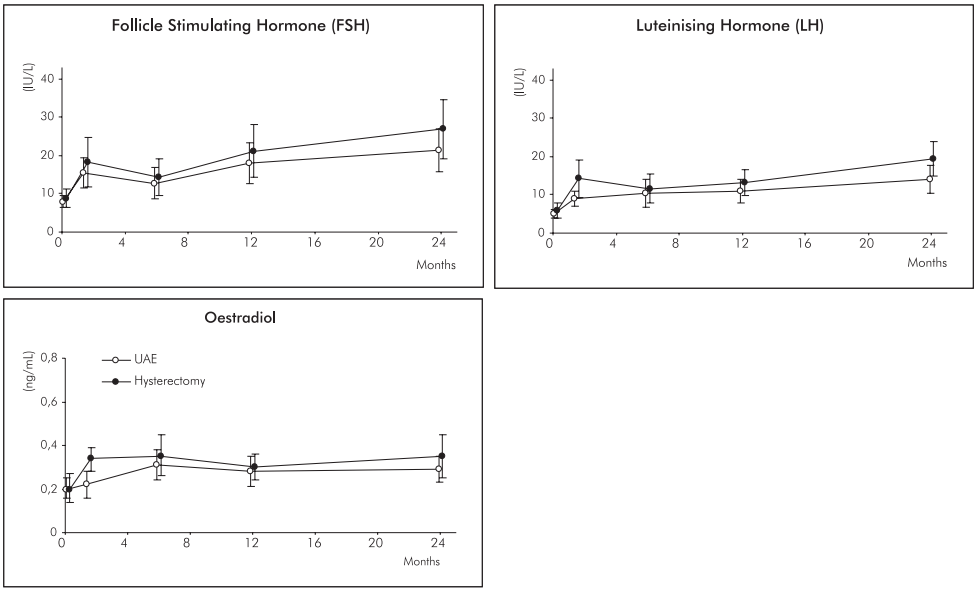
Between March 2002 and February 2004 177 patients (out of 349 eligible patients) agreed to participate in the study. 88 patients were randomized to the UAE group and 89 patients to the hysterectomy group. In the UAE group 81 patients underwent the allocated procedure compared to 75 in the hysterectomy group (Figure 1). Baseline characteristics did not differ between both groups (Table 2). At randomization 2 patients had had a unilateral oophorectomy previously (both >10 years ago). Their baseline FSH values were 6.0 IU/l and 8.5 IU/l. They were both randomized to the UAE group. In the UAE group, the procedure failed bilaterally in 4 cases. These patients subsequently had a hysterectomy, but were followed up in the UAE group (in the intention to treat analysis). In the follow up period of 24 months 15 additional patients had a secondary hysterectomy after UAE due to clinical failure [9].

UAE patients resumed having menstrual periods on average 24.4 days (SD: 24.4; median: 24 days; range: 0-172) after the procedure. Two patients did not have menstrual periods anymore after undergoing UAE.

HORMONAL PARAMETERS

Figure 2 displays mean values (with 95% Confidence Intervals (95%CI)) of FSH, LH and oestradiol over time for each treatment. Pre-treatment FSH measurements were not available for 3/75 hysterectomy patients. After treatment, FSH-values increased in both groups, peaked at 6 weeks, decreased until 6 months and then increased again slowly until 24 months. FSH levels after treatment were consistently higher after hysterectomy than after

FIGURE 2. FSH, LH and oestradiol over time



UAE, but the repeated measurement analysis revealed no significant differences between the groups (FSH: p=0.41; LH: p=0.16; oestradiol: p=0.12). Table 3 lists average differences between baseline values for each group and estimates at 6 weeks and 6, 12, 24 months after treatment. Statistically significant changes in the within group analysis are indicated in bold. In general, FSH increased significantly over time within the groups compared to

TABLE 3. Change of menopausal scores, FSH, LH, oestradiol and AMH at 6 weeks and 6, 12, 18, 24 months compared to baseline

	6 weeks change				6 months change			
	UAE	Hyst.	Difference (95%CI)	p-value	UAE	Hyst.	Difference (95%CI)	p-value
Menopause questionnaires								
Kupperman (0-51)	**-2.5**	**-2.4**	0.1 (-2.2 to 2.5)	0.91	**-2.0**	**-3.0**	-1.0 (-3.3 to 1.3)	0.40
Wiklund (0-51)	**-2.2**	**-2.5**	-0.3 (-2.9 to 2.2)	0.80	-1.5	**-3.0**	-1.5 (-4.2 to 1.2)	0.27
Oldenhave								
-Vasomotor (0-6)	0.1	-0.4	-0.5 (-1.0 to 0.01)	0.053	0.2	-0.1	-0.3 (-0.8 to 0.3)	0.30
-Vaginal dryness (0-3)	-0.1	-0.2	-0.1 (-0.4 to 0.2)	0.61	-0.1	0.1	0.2 (-0.1 to 0.4)	0.24
-Atypical symptoms (0-63)	**-3.6**	**-4.5**	-0.9 (-3.5 to 1.8)	0.53	**-4.0**	**-5.6**	-1.6 (-4.3 to 1.0)	0.22
Hormone levels								
FSH (IU/l)	**7.2**	**9.8**	2.7 (-4.2 to 9.5)	0.44	4.8	**6.6**	1.9 (-4.5 to 8.2)	0.56
LH (IU/l)	**3.8**	**8.0**	4.2 (-0.6 to 9.0)	0.09	**5.3**	**5.8**	0.5 (-4.8 to 5.8)	0.86
Oestradiol (nmol/l)	0.03	**0.13**	0.10 (-0.01 to 0.21)	0.07	**0.12**	**0.15**	0.03 (-0.10 to 0.17)	0.63
AMH (mg/l)	**-0.63**	-0.08	0.54 (0.18 to 0.92)	0.005	**-0.27**	**-0.14**	0.14 (-0.40 to 0.69)	0.60
AMH (mg/l) versus expected	**-0.62**	-0.07	0.54 (0.18 to 0.92)	0.005	**-0.23**	-0.09	0.14 (-0.40 to 0.68)	0.61

FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; AMH: Anti Mullerian Hormone. Statistically significant (p<0.05) change in the within group analysis is indicated in **bold** (Wilcoxon test)

baseline values (except for 6 months in the UAE group). LH increased significantly at all times within both groups. Average oestradiol levels increased significantly, except for 6 weeks after treatment in the UAE group. Table 4 lists number of patients by FSH levels, time and treatment group. No differences between the two groups were observed. FSH-levels >40 U/l at 24 months follow up were observed in 14/80 (17.5%) UAE patients compared to 17/73 (23.3%) hysterectomy patients (RR= 0.75; 95%CI: 0.40-1.41; p=0.37). Hormonal Replacement Therapy was used at 24 months follow up by five women (3 in UAE group and 2 in hysterectomy group).

Multiple logistic regression analysis on FSH >/< 40 IU/L revealed only age >45 at baseline (OR: 4.46; 95%CI: 1.79-11.14; p=0.001) to be significantly associated with FSH levels >40 IU/L after treatment. Treatment allocation (UAE/hysterectomy) was not associated with this outcome (p=0.38). Separate analyzes per treatment group revealed no treatment related variables to be predictive of ovarian failure (i.e. FSH >40 IU/L).

Analysis of AMH was based on 63 included patients (30 UAE vs. 33 hysterectomy) of whom pre-treatment serum was available. The mean age of these 63 patients was not significantly different between the groups (UAE: 45.0; hysterectomy: 45.2; p=0.84). The same accounts for mean baseline FSH (UAE: 7.7 IU/l; hysterectomy: 7.9 IU/l; p=0.95). None of the patients in either group had had a uni- or bilateral oophorectomy previously or during hysterectomy. In the UAE group 6 women (20%) had a secondary hysterectomy between 12 and 24 months follow up. Only AMH values after the secondary hysterectomy were

12 months change				18 months change				24 months change			
UAE	Hyst.	Difference (95%CI)	p-value	UAE	Hyst.	Difference (95%CI)	p-value	UAE	Hyst.	Difference (95%CI)	p-value
-0.5	**-1.9**	-1.4 (-4.0 to 1.1)	0.28	-0.9	-1.7	-0.8 (-3.4 to 1.8)	0.56	-0.5	-0.23	0.3 (-2.6 to 3.2)	0.84
-0.4	-1.9	-1.5 (-4.4 to 1.4)	0.31	-0.5	-1.2	-0.6 (3.7 to 2.5)	0.68	-0.05	0.05	0.1 (-3.1 to 3.3)	0.95
0.4	0.1	-0.3 (-0.9 to 0.3)	0.32	**0.5**	0.12	-0.4 (-1.0 to 0.2)	0.22	**0.6**	**0.5**	-0.1 (-0.7 to 0.5)	0.71
-0.02	0.1	0.2 (-0.1 to 0.4)	0.25	-0.1	**0.2**	0.2 (-0.02 to 0.5)	0.07	-0.01	0.1	0.1 (-0.2 to 0.4)	0.64
-3.0	**-6.1**	-3.1 (-5.7 to -0.5)	0.02	**-3.7**	**-6.0**	-2.3 (-5.2 to 0.6)	0.11	**-3.9**	**-5.1**	-1.2 (-4.2 to 1.8)	0.42
9.6	**13.0**	-3.4 (-4.2 to 11.1)	0.38	NA	NA	NA	NA	**13.3**	**17.8**	4.6 (-4.1 to 13.3)	0.30
5.8	**7.3**	-1.5 (-2.9 to 5.9)	0.50	NA	NA	NA	NA	**8.9**	**12.5**	3.5 (-2.0 to 9.0)	0.21
0.09	**0.11**	-0.02 (-0.08 to 0.12)	0.69	NA	NA	NA	NA	**0.09**	**0.15**	0.06 (-0.08 to 0.19)	0.42
-0.41	-0.01	0.40 (-0.16 to 0.95)	0.16	NA	NA	NA	NA	**-0.61**	**-0.31**	0.30 (-0.24 to 0.85)	0.27
-0.31	-0.09	0.39 (-0.16 to 0.94)	0.16	NA	NA	NA	NA	**-0.42**	-0.12	0.29 (-0.24 to 0.83)	0.28

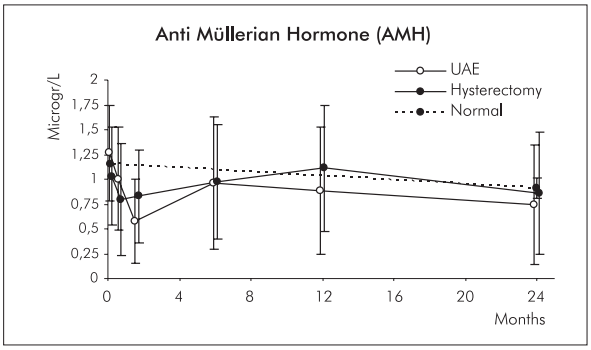


FIGURE 3. AMH over time. Data for the normal decrease were derived from 'van Rooij et al., 2005. [31]'

excluded from further analysis. Figure 3 displays means (with standard errors) of AMH-values over time, together with the natural decrease of AMH as expected for the age-range of our patients. Follow-up samples were available for 61/63 (97%) patients (at 6 months), 60/63 (95%) patients (at 12 months) and 53/63 (84%) patients (at 24 months). In hysterectomy patients mean AMH-values decreased until 6 weeks after treatment. Between 6 weeks and 12 months mean AMH-values recovered to the expected (normal) values and remained that way until 24 months follow up. Mean AMH values of UAE patients decreased initially with a slight recovery between 6 weeks and 6 months, but remained significantly under the expected value range until 24 months follow up. Repeated measurements analysis revealed no differences between the groups.

Table 3 displays mean change scores for AMH levels compared to baseline (except for the measurement 1 day after the procedure, which was only used for plotting purposes). Statistically significant changes in the within group analysis are indicated in bold in Table 3. AMH levels in the UAE group decreased significantly at all time points, both compared to baseline and compared to expected levels. In the hysterectomy group the change from baseline was only significant at 6 and 24 months (p=0.010 and p=0.027), while none of

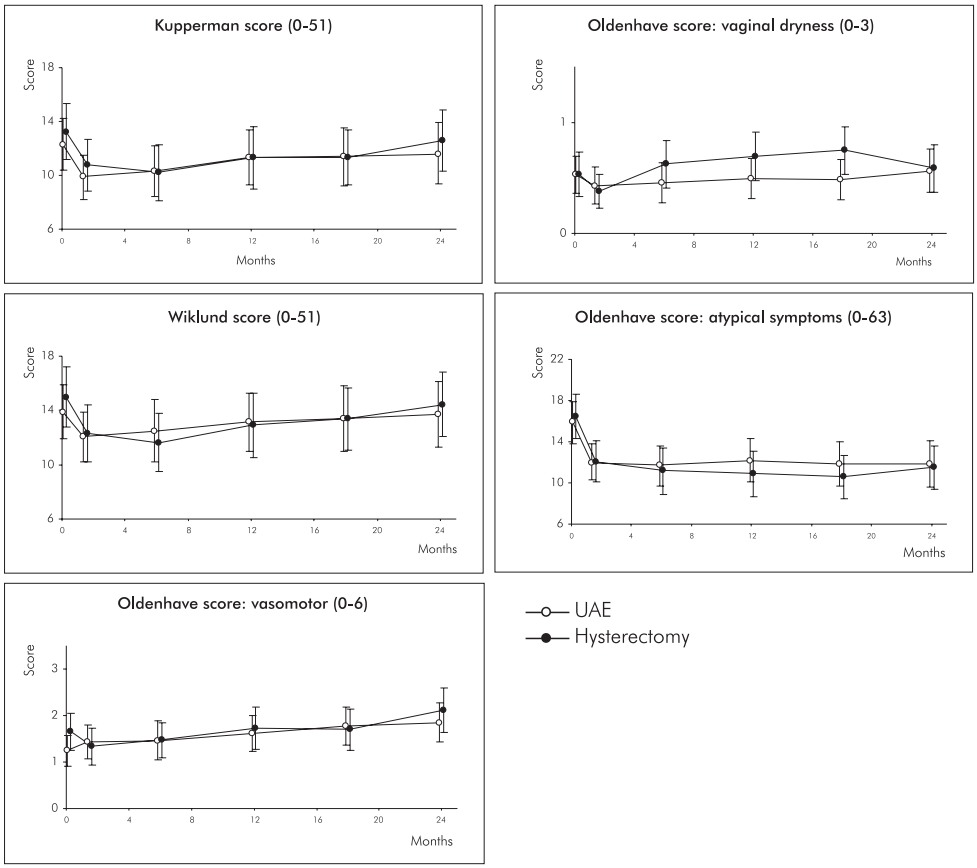
TABLE 4. Comparison of ranges of FSH-values between treatment groups at 6 weeks and 6, 12, 24 months after treatment

	6 weeks after treatment			6 months after treatment		
FSH (IU/l)	UAE (n=79) n (%)	Hyst. (n=69) n (%)	p-value*[1]	UAE (n=78) n (%)	Hyst. (n=69) n (%)	p-value*[1]
<10	48 (61)	45 (65)	0.66	57 (73)	48 (70)	0.99
10-20	11 (14)	10 (15)		9 (12)	9 (13)	
20-30	5 (6)	1 (1)		2 (3)	2 (3)	
30-40	5 (6)	3 (4)		3 (4)	3 (4)	
>40	10 (13)	10 (15)		7 (9)	7 (10)	

Hyst.: hysterectomy; FSH: Follicle Stimulating Hormone. *[1] Fisher's exact

the observed values were significantly lower than the expected decrease. In the between group analysis, there was only a significant difference at 6 weeks (p=0.005).

FIGURE 4. Menopause scores over time (Kupperman, Wiklund and Oldenhave)



12 months after treatment			24 months after treatment		
UAE (n=74) n (%)	Hyst. (n=73) n (%)	p-value*[1]	UAE (n=80) n (%)	Hyst. (n=73) n (%)	p-value*[1]
43 (58)	42 (58)	0.48	41 (51)	38 (52)	0.87
12 (16)	12 (16)		12 (15)	9 (12)	
3 (4)	4 (5)		8 (10)	6 (8)	
7 (9)	2 (3)		5 (6)	3 (4)	
9 (12)	13 (18)		14 (18)	17 (23)	

Univariate analysis on decrement of AMH 24 months after treatment revealed no variables to be predictive (all: $p>0.10$). As demonstrated in Table 3 as well, treatment allocation was not associated with the outcome ($p=0.27$).

MENOPAUSAL PARAMETERS

Baseline menopausal scores were not available for 11/81 (13.6%) UAE and 9/75 (12.0%) hysterectomy patients. Response rates to the follow-up questionnaire were 155/156 (99%, 6 weeks), 151/156 (97%, 6 months), 151/156 (97%, 12 months), 150/156 (96%, 18 months) and 154/156 (99%, 24 months) respectively.

In Figure 4 the mean menopausal scores (95%CI) of both treatments are plotted over time for the Kupperman, Wiklund and Oldenhave (vasomotor, vaginal dryness and atypical symptoms) scores. Repeated measurement analysis revealed no differences between the groups (Kupperman: $p=0.65$; Wiklund: $p=0.83$; Oldenhave vasomotor: $p=0.63$; Oldenhave vaginal dryness: 0.63; Oldenhave atypical symptoms: $p=0.63$). The baseline scores did not differ significantly between groups.

Average differences with baseline values for each group at 6 weeks and 6, 12, 24 months follow up are listed in Table 3. Only the Oldenhave atypical symptoms at 12 months after treatment were significantly different between both groups.

Within group analysis revealed several significant changes compared to baseline (indicated in bold in Table 3). The Kupperman and Wiklund scores decreased the most with significant changes in the short term. The Oldenhave vasomotor score was significantly increased in both groups at 24 months follow up. Vaginal dryness was only significantly increased at 18 months follow up in the hysterectomy group and atypical symptoms decreased significantly in both groups at all occasions.

DISCUSSION

The effect of UAE on the ovaries in comparison to hysterectomy has not been established earlier. Ovarian function after hysterectomy has been investigated extensively. Some studies have shown that hysterectomy affects the age at which the onset of menopause occurs [35] and that hysterectomy may increase the incidence of menopausal symptoms [36-39]. Also, FSH and/or LH levels have been shown to increase significantly after hysterectomy [10-14] although others did not confirm these findings [40;41].

In contrast, the present knowledge on the effect upon ovarian function after UAE is limited, and derives mainly from case-reports and small series. Permanent loss of ovarian function

after UAE resulting in menopause has been reported in several studies [18-21]. This complication seems to occur mainly in women > 45 years of age [20;42]. Transient ovarian failure has also been described [43;44], but other studies did not show any untoward effects on ovarian function from UAE [45-49]. Ovarian damage is thought to occur after UAE because of passage of embolization particles through anastomotic vessels between uterine and ovarian arteries, causing hypoxic ovarian damage and tissue loss [50]. Indeed, it has been confirmed that embolization particles can be found at histopathologic examination of ovarian tissue after UAE [51]. Furthermore, loss of ovarian perfusion, as demonstrated by sonographic assessment, directly after treatment in a substantial number of patients has been observed [52].

In our study, very few differences in effect on ovarian reserve were found between UAE and hysterectomy: both treatments cause damage to the ovaries, as substantiated by a significant rise in FSH and LH serum levels. The drop in AMH levels immediately after treatment represents the loss of ovarian tissue, probably as a result of vascular compromise with ensuing ischemia, either by inadvertent embolization of ovarian vasculature in UAE, or by compromising ovarian bloodflow by ligating anastomosing vessels during hysterectomy. Results of indicators of ovarian reserve tests tend to partially recover after both treatments, supporting earlier observations that ovarian failure may be transient [43;44]. After the (partial) recovery of ovarian function, the decrement is only significant after UAE when compared to the expected decrement due to ageing, thereby indicating that UAE might be even more harmful to ovarian reserve status than hysterectomy.

Multiple regression analysis revealed that higher age (>45 years of age) predicted the occurrence of elevated post-menopausal FSH values. This indicates that women with low ovarian reserve (older women and women with higher FSH values at baseline) are prone to develop a menopausal state. However, the decrease in AMH in the first 24 months, which was not correlated with age, indicates that every woman experiences loss of ovarian reserve. For older women with less ovarian reserve, this means that menopause is more likely to occur. For younger women, however, relative damage occurs, which does not result in menopause, but which might impair ovarian reserve and may affect future prospects of becoming pregnant. Although this relative damage may be missed altogether by low-sensitivity diagnostic tests such as FSH measurements and by assessment of clinical signs and symptoms, analysis of AMH patterns, however, reveal its presence.

Reduction of ovarian reserve is of special importance when UAE is used in the treatment of women desiring future fertility, which is now still being discouraged [44;50;53;54]. The impact on future fertility was not the scope of our trial, which excluded women with a desire for future pregnancy. Although UAE has been advocated by some to be used in women who do wish to conceive, our results discourage this view.

Our patients had no alternative other than hysterectomy, since other treatment options (i.e. medical therapy, endometrial ablation or myomectomy) were not possible or had already provided insufficient clinical results. Therefore, ovarian damage could not be avoided. With the proper indication, UAE might provide a suitable alternative for hysterectomy, since no differences in impact on ovarian reserve between the treatments were found. For patients with less severe fibroid related complaints or patients with the desire for future fertility, one should keep in mind that ovarian damage may occur when UAE is undertaken, and might be avoided with other treatment choices.

In contrast to a rise in average FSH levels, no significant increase in menopausal symptoms was observed, except for the Oldenhave vasomotor symptoms. This is probably consistent with the absence of low oestradiol levels as found in the present study. In contrast, oestradiol levels increased, probably as a result from hyper-stimulation of the ovaries by elevated FSH values as found in our study [23].

A limitation of our study was the inability to obtain serum samples strictly at the third day of the menstrual cycle to obtain a standardized parameter for ovarian reserve [55]. This standardization was sometimes impossible because of permanent vaginal blood loss prior to the intervention, absence of menstrual bleeding in post hysterectomy patients or irregular menstrual cycles. Thereby average FSH values might be higher by inclusion of mid-cycle samples. However, FSH values normally do not reach the cut-off level we used as indicator of menopause (i.e. >40 IU/L) [23].

Furthermore, we did not have a control group for the occurrence of ovarian ageing over time. However, AMH values in both groups dropped dramatically immediately after treatment in comparison to the normal (expected) decrease of AMH for our patients' age group (Figure 3). This indicates instant ovarian damage that may have been caused by demise of the follicle cohort responsible for the AMH levels. The mechanism of (partial) recovery of the AMH levels thereafter may be attributed by restoration of the follicle cohort from the primordial follicle pool. However, since AMH levels do not reach the expected level over time for the UAE group, it may be suggested that also the primordial pool has suffered irreparable damage in this group.

Furthermore, our study population was relatively old. The occurrence of a significant and permanent drop in AMH-levels in the UAE group might be different in a younger age group, i.e. the age group of particular interest when desire for future fertility is at stake. We encourage future studies to address these matters.

In conclusion, both UAE and hysterectomy affect ovarian reserve. No differences between both treatments on ovarian function were observed, however. Especially when future pregnancy is desired UAE should only be offered after appropriate counseling.

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RADIOLOGY, ACCEPTED

8

HEALTH RELATED QUALITY OF LIFE AND PATIENTS' SATISFACTION AFTER UTERINE ARTERY EMBOLIZATION VERSUS HYSTERECTOMY IN THE TREATMENT OF SYMPTOMATIC UTERINE FIBROIDS: RESULTS FROM THE RANDOMIZED EMMY TRIAL

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ABSTRACT

Purpose

To prospectively evaluate health related quality of life (HRQOL) outcomes for uterine artery embolization (UAE) and hysterectomy up to 2 years after the intervention in terms of general health (mental and physical health), urinary dysfunction, defecation dysfunction and overall patients' satisfaction.

Methods

Ethics committee approval and informed consent were obtained for the EMMY (EMbolization versus hysterectoMY) trial, a multi-center randomized clinical trial with a follow up period of two years. 177 women (mean age: 45.0 years; SD: 4.5) with uterine fibroids and heavy menstrual bleeding, who were to be scheduled for a hysterectomy were randomly allocated UAE (n=88) or hysterectomy (n=89). HRQOL was measured at 6 occasions during a two years follow up period using validated questionnaires: the Medical Outcome Study Short Form-36 (SF-36, both the mental component summary (MCS) and the physical component summary (PCS)), the health utility index (HUI-3), the euro quality of life 5D (EQ-5D), the urogenital distress inventory (UDI), the incontinence impact questionnaire (IIQ) and the defecation distress inventory (DDI). Satisfaction was assessed using a 7-point Likert scale. A repeated measurements analysis was performed for the between group evaluation. For within group analysis paired t-tests were performed. Satisfaction was analyzed using a Fishers exact test.

Results

The SF-36 (MCS and PCS), HUI-3, EQ-5D and UDI all improved significantly in both groups from 6 months onward (all: $p<0.05$). DDI improved significantly only in the UAE group from 6 months follow up onward (all: $p<0.05$). No differences between both groups were observed, except for PCS scores at 6 weeks follow up: UAE patients had significantly better scores than hysterectomy patients ($p<0.0001$). PCS improvement at 24 months was significantly higher for employed patients ($p=0.035$). Hysterectomy patients were significantly more satisfied than UAE patients at 24 months follow up ($p=0.020$). High increments in SF-36 MCS at 24 months were associated with higher satisfaction ($p=0.001$).

Conclusion

Both UAE and hysterectomy improved HRQOL substantially. No differences were observed between both groups regarding HRQOL at 24 months follow-up. Based on HRQOL results, UAE is a good alternative to hysterectomy.

INTRODUCTION

In the United States approximately 600.000 hysterectomies are performed each year, mostly for symptomatic uterine fibroids [1]. An alternative treatment to hysterectomy for this indication is provided by uterine artery embolization (UAE), which was introduced in 1995 [2]. Despite its clinical application for more than a decade, the risks and benefits of UAE in comparison to hysterectomy based on a randomized clinical trial have remained largely unknown, and evidence on its efficacy and safety derived from uncontrolled case-series and one small randomized trial [3-8]. To evaluate the efficacy of UAE in comparison to hysterectomy as standard treatment for uterine fibroid related menorrhagia, we initiated a prospective, multi-center, randomized clinical trial comparing both treatments. In our trial major complication rates were low in both groups, peri-procedural complication rates did not differ between both treatments and UAE was demonstrated to prevent a subsequent hysterectomy in 76.5% of cases [9;10].

Although hysterectomy is a definite solution for fibroid related complaints, its invasiveness, duration of recovery and possible long term risks, warrant a careful examination of alternatives such as UAE. Since UAE and hysterectomy are interventions which are very different from each other, comparison can be difficult. One measure which is very suitable for the comparison of both treatments is health related quality of life (HRQOL).

Thus, the purpose of our study was to prospectively evaluate HRQOL outcomes for UAE and hysterectomy up to 2 years after the intervention in terms of general health (mental and physical health), urinary dysfunction, defecation dysfunction and overall patients' satisfaction.

METHODS

The EMMY-trial was funded by ZonMw 'Netherlands Organization for Health Research and Development', a semi-governmental organization that promotes quality and innovation in the field of health research and health care, initiating and fostering new developments. Boston Scientific partly sponsored the embolic agent used in this trial. Both ZonMw and Boston Scientific were not involved in designing and conducting the trial, had no access to the data, were not involved in analyzing the data or writing the manuscript and did not approve the manuscript. None of the authors are employed by or have commercial interest in either ZonMw or Boston Scientific.

STUDY DESIGN AND PATIENTS

The trial characteristics have been described in detail elsewhere and will be summarized here briefly [9;10]. The EMMY (EMbolization versus hysterectoMY) study is a multi-center, randomized clinical trial, conducted in the Netherlands. Patients visiting the gynecological outpatient clinics were asked to participate if they 1) were pre-menopausal, 2) were diagnosed with uterine fibroids, 3) had menorrhagia, 4) had no other regular treatment options than a hysterectomy and 5) had no desire for future pregnancy.

After written informed consent had been obtained, patients were randomized (1:1) to UAE or hysterectomy. Randomization was computer based and stratified for participating hospital. Randomization was carried out in the coordinating hospital (Academic Medical Centre, Amsterdam)

The study was approved by the Central Committee Involving Human Subjects (www.ccmo.nl) and by local ethics committees of participating hospitals.

STUDY INTERVENTIONS

Uterine artery embolization

UAE was performed under local anesthesia. Polyvinyl alcohol particles (PVA, Contour, Boston Scientific, Beek, The Netherlands) with a size of 355-500 μm were used in all procedures. Only if an anastomosis with the ovarian artery was observed 500-700 μm particles were used. PVA, mixed with contrast medium and saline, was injected into each uterine artery until parenchyma filling of the fibroids had stopped (target embolization) or until the main uterine artery was blocked with stasis of contrast (selective embolization). After the procedure women were admitted to the gynecology ward for post procedural care. All patients were advised to stay in the hospital for at least one night.

UAE was performed by several interventional radiologists who did arterial embolizations on a regular basis and had experience in at least 15 UAE procedures. If this was not the case, the interventional radiologist was supervised by an interventional radiologist that qualified according to the above mentioned criteria.

Hysterectomy

The type of hysterectomy and the route of access were left at the discretion of the attending gynecologist and could be abdominal, vaginal or laparoscopic. Both supravaginal and total hysterectomies were allowed. The surgeons that performed the surgical procedures in our trial had done at least 50 hysterectomies, or were supervised by one that had.

STUDY MEASURES

Generic HRQOL

Patients' health status and HRQOL was assessed by questionnaires at baseline and every 6 months after the procedure up to 2 years after treatment, with an extra questionnaire at 6 weeks after the procedure. All questionnaires were identical. Socio-demographic data were assessed only at baseline.

Six validated questionnaires were used to assess health status and HRQOL: the Medical Outcome Study Short Form 36 (SF-36), the EuroQOL 5 dimension 3 level version (EQ-5D), the Health Utilities Index Mark 3 (HUI-3), the urogenital distress inventory (UDI), the Incontinence Impact Questionnaire (IIQ) and the defecation distress inventory (DDI).

The SF-36 questionnaire is a health survey frequently used in assessing health related quality of life alongside clinical studies [11;12]. It comprises of 36 questions summarized in the following 8 domain scores of physical and mental functioning: physical functioning, role functioning physical as well as emotional, social functioning, bodily pain, mental health, vitality and general health perceptions. The 8 domain scores can be summarized in two measures: the physical component summary score (PCS) and the mental component summary score (MCS), which are derived using weighted averages of the individual domain scores [13]. The PCS and MCS provide scores ranging from 0-100 (100 indicating the optimal score).

The EQ-5D describes health status in terms of 5 dimensions (i.e. mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) [14;15]. Each dimension is described using three functional levels (i.e. 1 = no problems, 2 = moderate problems, and 3 = severe problems). These functional levels are transformed into a score ranging from 0 to 1.0 (1.0 being the optimal score) by an algorithm that adjusts for age [16].

The HUI-3 (Health Utilities Index Mark 3) is another measure of functional health and health related quality of life that is widely used as outcome measure in clinical and population studies [17]. HUI-3 consist of the following eight dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each question has 5 or 6 possible answers (levels), varying from highly impaired to normal. The 8 questions yield a score ranging from 0 (~ dead) to 1 (~ perfect health).

Urinary function and defecation

The Urogenital Distress Inventory (UDI) and the Incontinence Impact Questionnaire (IIQ) were designed by Shumaker et al [18] to assess impact of symptoms associated with incontinence or genital prolapse on well-being and daily activities and emotions. We used the total 19 items UDI score and the short version of the IIQ: the IIQ-7, which comprises of 7 items from the original 30 items [19]. These disease-specific questionnaires have shown to be especially valid

for use in women previously diagnosed with urinary incontinence. The internal consistency of the UDI has shown to be moderately high and the internal consistency of the IIQ-7 has shown to be good [20]. UDI and IIQ scores range from 0-100. A higher UDI/IIQ score indicates a worse outcome. The IIQ score was only administered to patients who reported complaints of urinary incontinence.

The defecation distress inventory (DDI) is a Dutch validated questionnaire that was developed analogous to the UDI [21]. The DDI can be used to assess the presence and experienced burden of defecation symptoms. The DDI score ranges from 0-100. A higher DDI score indicates a less favorable outcome.

At baseline and at all follow visits patients were asked to rate the overall quality of their urinary and stool function: 'very good', 'good', 'fairly good', 'not good, nor bad', 'fairly bad', 'bad' or 'very bad'.

Furthermore, an inquiry was made if patients used pads for urinary incontinence or laxatives at all time points.

Satisfaction

Finally patients were asked in every follow up questionnaire to indicate how satisfied they were with the received treatment(s): 'very satisfied', 'satisfied', 'fairly satisfied', 'not satisfied, nor unsatisfied', 'fairly unsatisfied', 'unsatisfied' or 'very unsatisfied'.

SAMPLE SIZE, ENDPOINTS, POST-HOC POWER ANALYSIS

The sample size was based on the primary endpoint of the clinical study: the elimination of menorrhagia in such way that hysterectomy could be avoided in the UAE group in at least 75% of patients, not on HRQOL [10]. For that reason, we performed a post-hoc power analysis on SF-36 PCS and MCS summary measures. Since a HRQOL mean score difference of at least 5 (0-100) points should be considered a meaningful difference [22], power was calculated using the following equivalence assumptions:

1: null-hypothesis: mean MCS [PCS, respectively] differs at least 5 points between UAE and hysterectomy; 2: alternative hypothesis: mean MCS [PCS, respectively] differs less than 5 points between UAE and hysterectomy. As our results will show, the observed mean difference in MCS [PCS] score between strategies at 24 months follow up is: +1.0 [-0.7, respectively]. The following assumptions were used: alpha=0.05 (one-sided); delta (equivalence range) =5.0. This produced a post hoc power of 76% for MCS and 93% for PCS to reject the null hypothesis.

STATISTICAL ANALYSES

A random sample of 10% of the questionnaires was visually double checked by an independent investigator revealing a false entry level of 0.3%. Analyses were done using SPSS statistical software (version 11.5.1).

Study outcomes were analyzed according to original treatment assignment (intention to treat). Differences in baseline characteristics were tested with multiple logistic regression analysis with randomization outcome as the dependent variable.

Mean HRQOL scores were plotted for both groups for baseline and all follow up moments. Repeated measurement analysis was performed to evaluate longitudinal differences between treatment strategies. Differences in HRQOL between the groups at the separate time points were assessed with Student's t-tests. The change of HRQOL compared to baseline was assessed with paired t-tests in each treatment group separately, for all follow up moments.

Patients' satisfaction between treatment groups was compared using Fisher's Exact test.

Self-reported quality of urinary and stool function at follow up was compared to baseline and yielded one of three possible answers: quality was worse, the same or better. Differences between treatment groups were compared using the Chi-square tests.

To test the influence of improvement in SF-36 MCS and PCS on satisfaction, logistic regression analysis was performed. For this purpose, satisfaction ratings at 24 months were dichotomized into 'satisfied' (patients who answered 'very satisfied' and 'satisfied') versus 'less than satisfied' (patients whose answer ranged from 'moderately satisfied' to 'very unsatisfied').

To evaluate the effect of baseline variables on HRQOL change at 24 months compared to baseline (for SF-36 MCS and PCS), multiple linear regression analysis was performed with variables yielding p-values <0.1 in the univariate analysis. The following variables were included in the univariate analysis: intended treatment (UAE/hysterectomy), age (continuously), BMI (continuously), ethnicity (Caucasian/non-Caucasian), parity (parous/non-parous), current smoking (yes/no), educational level (intermediate level -or higher- versus lower level), married (yes/no), paid work (yes/no), comorbidity (yes/no), uterine volume (continuously), number of fibroids (continuously), previous iron-substitution therapy/blood transfusion (yes/no), previous surgical treatment (yes/no), any previous treatment (yes/no), duration of menorrhagia symptoms (continuously), anemia before treatment (yes/no), baseline SF-36 MCS (continuously, not on MCS change outcome) and baseline SF-36 PCS (continuously, not on PCS change outcome).

A subgroup analysis was performed on longitudinal differences in HRQOL between UAE and hysterectomy, by excluding the subgroup of patients treated with UAE who later received hysterectomy.

Finally we performed a subgroup analysis within the UAE subgroup comparing women who underwent an UAE with/without a subsequent hysterectomy (for failed UAE or insufficient treatment effect) for SF-36 MCS and PCS scores.

A p-value of <0.05 (two sided) was considered statistically significant in all analyses.

RESULTS

PATIENTS

Patients were enrolled between March 2002 and February 2004. Twenty-eight of the thirty-four participating hospitals included patients. Of 349 eligible patients, 177 were randomized: 88 were allocated UAE and 89 hysterectomy (Figure 1). The majority of patients refusing participation did so for a strong preference for hysterectomy (58%). After randomization 7 patients in the UAE group and 14 patients in the hysterectomy group refused the allocated treatment and withdrew from the study. Patients who refused the assigned treatment were comparable to participating patients in terms of age (mean: 45.3 years; SD: 4.9; p=0.59), race (white: 13/21; black: 8/21; p=0.09), BMI (mean: 24.7; SD: 4.5; p=0.18), parity (parous: 16/21; p=0.63), symptoms (for all symptoms mentioned in Table 1: $p>0.05$) and duration of symptoms (mean: 32.8 months; SD: 26.1; p=0.62).

The mean age of the participating patients was 44.6 years (UAE group) and 45.4 years (hysterectomy group) (Table 1). Participants were predominantly white: 61.4% and 64.0% for UAE and hysterectomy respectively.

Most patients (85.3%) had already received one or more treatments before study enrolment. Patients suffered from menorrhagia for a median of 24 months. Other symptoms besides menorrhagia were prevalent. The majority of women had multiple fibroids. Logistic regression analysis did not reveal any baseline characteristics to be predictive of treatment allocation, thus confirming successful randomization.

CLINICAL OUTCOME

The procedures have earlier been described in detail [9]. Most hysterectomies were performed transabdominally (84.0%). A total of 19 (23.5%) secondary hysterectomies were performed in the UAE group: 4 because of bilateral UAE failure and another 15 because of clinical failure during 24 months of follow up [10].

FIGURE 1. Flow diagram

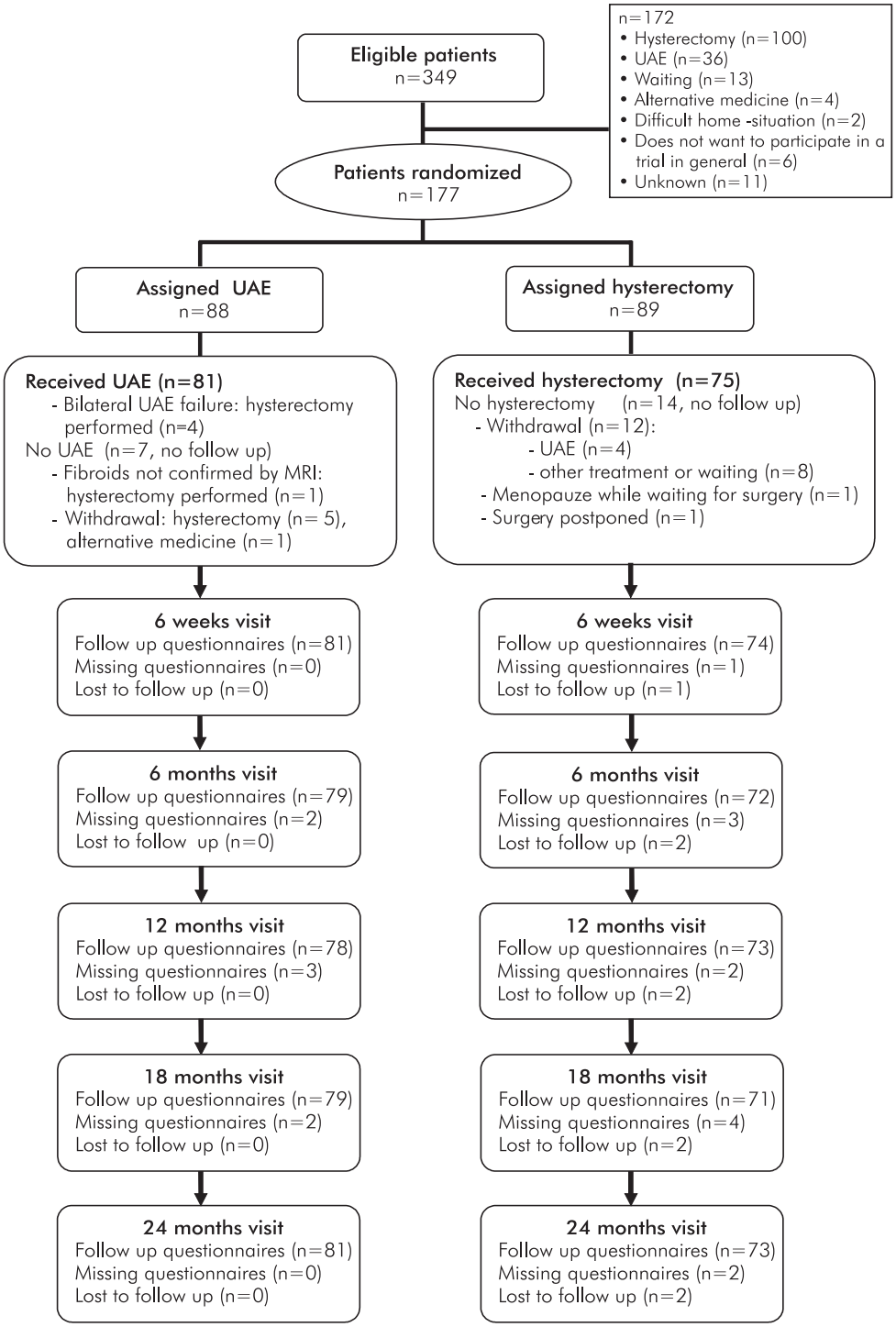


TABLE 1. Baseline and procedural characteristics

	UAE n=88 n (%)	Hysterectomy n=89 n (%)
Age (years)		
Mean (SD)	44.6 (4.8)	45.4 (4.2)
Body Mass Index (weight (kg) / length $(m)^2$)		
Mean (SD)	26.7 (5.6)	25.4 (4.0)
Parity		
0	30 (34.1)	20 (22.5)
>1	58 (65.9)	69 (77.5)
Ethnicity		
Black	24 (27.3)	20 (22.5)
White	54 (61.4)	57 (64.0)
Other	10 (11.4)	12 (13.5)
Marital status		
Single	16 (18.2)	13 (14.8)
Married	55 (62.5)	54 (61.4)
Living Apart Together	5 (5.7)	4 (4.5)
Divorced	12 (13.6)	15 (17.0)
Widow	0 (0)	2 (2.3)
Employment status		
Employed	68 (77.3)	69 (78.4)
Unemployed	20 (22.7)	19 (21.6)
Smoking status		
Current smoker	21 (23.9)	23 (25.8)
Former smoker	11 (12.5)	14 (15.7)
Non-smoker	56 (63.6)	52 (58.4)
Highest educational level		
Elementary school	3 (3.4)	6 (6.9)
Lower vocational, lower secondary school	29 (33.0)	32 (36.8)
Intermediate and higher vocational, higher secondary school	26 (29.5)	27 (31.0)
College/University	28 (31.8)	22 (25.3)
Other	2 (2.3)	0 (0)
Previous treatment		
None	11 (12.5)	15 (16.9)
Hormonal	59 (67.0)	59 (66.3)
Non-Steroidal-Anti-Inflammatory-Drugs /Tranexaminacid	45 (51.1)	41 (46.1)
Iron-supplement/blood transfusion	50 (56.8)	52 (58.4)
Surgical procedures	17 (19.3)	11 (12.4)
Symptoms		
Menorrhagia	88 (100)	89 (100)
Dysmenorrhoea	47 (53.4)	50 (56.2)
Pain (not during menstruation)	15 (17.0)	14 (15.7)
Anemia	43 (48.9)	42 (47.2)
Pressure symptoms	23 (26.1)	25 (28.1)
Other symptoms	6 (6.8)	11 (12.4)

-Continued **TABLE 1**

		UAE n=88 n (%)	Hysterectomy n=89 n (%)
Duration of symptoms (months)			
Median (range)		24 (3-250)	24 (4-240)
Number of fibroids			
Median (range)		2 (1-20)	2 (1-9)
Uterine volume (cm^3)			
Median (range)		321 (31-3005)	313 (58-3617)
Fibroid volume (dominant fibroid, cm^3)			
Median (range)		59 (1-673)	87 (4-1641)
Type of UAE			
Target embolization	Left uterine artery	65	-
	Right uterine artery	59	-
Selective embolization	Left uterine artery	8	-
	Right uterine artery	12	-
Type of hysterectomy		(n=4)	
Abdominal hysterectomy		(2)	63
Vaginal hysterectomy		(1)	8
Vaginal hysterectomy with morcellator		(1)	1
LH with morcellator		-	2
LAVH		-	1

QUALITY OF LIFE OUTCOMES

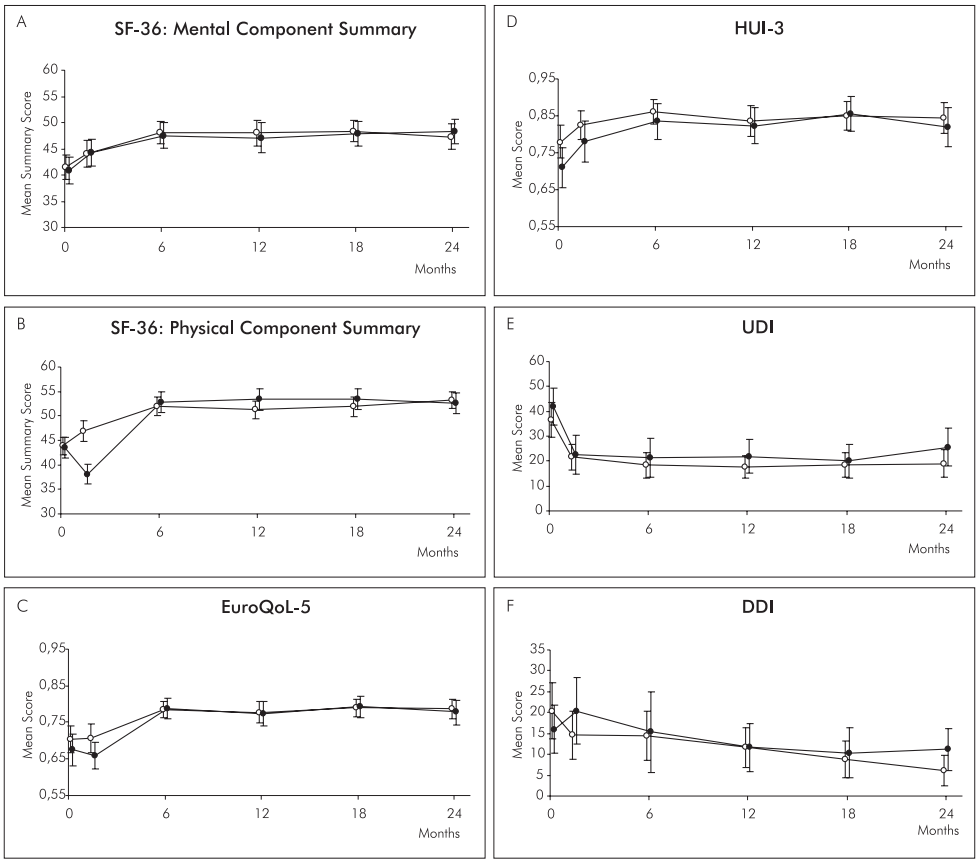
During 24 months follow up, 936 out of 957 (97.8%) mailed questionnaires were returned.

Generic HRQOL

Regarding mental health (SF-36 MCS), Physical health (SF-36 PCS), EuroQOL-5D (EQ-5D) and Health Utility Index (HUI-3) scores for both groups, baseline scores did not differ significantly (Figure 2A-D). Improvements in general HRQOL mainly occurred during the first 6 months after treatment. After this period, HRQOL scores stabilized in both groups without showing any significant difference between the treatment strategies (Table 2). Numbers in **bold** indicate a statistically significant ($p<0.05$) change from baseline in the within group analysis.

Comparison of the change in scores of all generic HRQOL measures (SF-36, EQ-5D, HUI-3) between the groups shows only the SF-36 physical component summary (PCS) to be significantly different at 6 weeks follow up ($p<0.0001$) (Table 2). All other changes did not differ significantly between the strategies. Within each treatment group, all general HRQOL measures improved significantly compared to baseline from 6 months onward. Repeated

FIGURE 2 A-F. Quality of life: intention to treat analysis



The figures display that UAE and hysterectomy display very similar patterns and that both improve during follow up compared to baseline, o = UAE, ● = Hysterectomy

measurement analysis revealed no longitudinal differences between the groups, not even so after excluding the 19 UAE patients who subsequently underwent a hysterectomy for persistent menstrual problems (data not shown).

Multiple linear regression analysis revealed no baseline variable to be associated with improvement of SF-36 MCS scores at 24 months. In contrast, being employed at baseline significantly enhanced SF-36 PCS at 24 months (Beta: 3.61; 95%CI: 0.26 to 6.96; p=0.035).

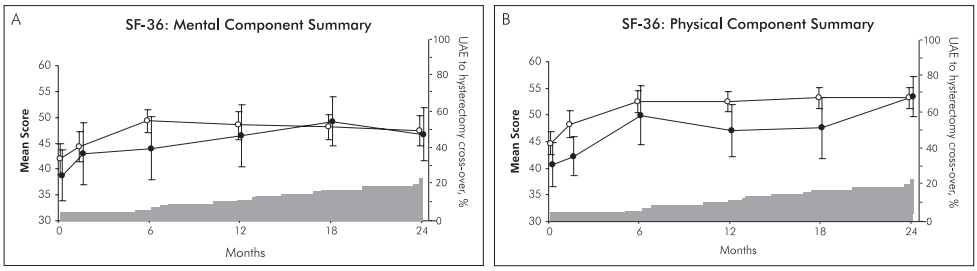
UAE patients who subsequently required a hysterectomy showed lower SF-36 PCS scores in the repeated measurements analysis (p=0.021) than those women undergoing UAE alone (Figure 3). For the SF-36 MCS this was not the case (p=0.319). Analysis of individual differences at various time points revealed that only the PCS at 6 weeks and at 12 months

TABLE 2. Quality of life change scores up to 2 years after UAE and hysterectomy

	UAE (n=81)	Hyst. (n=75)	Change score difference (95%CI)	p-value
			6 weeks change score	
MOS SF-36 MCS	2.65	2.78	0.013 (-4.24 to 4.50)	0.953
MOS SF-36 PCS	**3.09**	-5.96	-9.05 (-12.33 to -5.77)	<0.0001
HUI-3	**0.046**	**0.043**	-0.003 (-0.061 to 0.056)	0.932
EuroQoL-5	0.007	-0.027	-0.035 (-0.098 to 0.028)	0.278
UDI	**-14.31**	**-16.77**	-2.46 (-12.89 to 7.96)	0.641
IIQ*[1]	-10.12	-7.34	2.78 (-18.94 to 24.50)	0.781
DDI	-5.38	4.69	10.07 (-0.14 to 20.28)	0.053
			6 months change score	
MOS SF-36 MCS	**7.03**	**7.09**	0.061 (-3.99 to 4.11)	0.976
MOS SF-36 PCS	**8.05**	**10.21**	2.16 (-1.09 to 5.41)	0.192
HUI-3	**0.080**	**0.117**	0.037 (-0.026 to 0.101)	0.249
EuroQoL-5	**0.085**	**0.118**	0.034 (-0.030 to 0.097)	0.297
UDI	**-18.63**	**-18.76**	-0.13 (-11.65 to 11.39)	0.982
IIQ*[1]	-7.62	-11.43	-3.81 (-21.04 to 13.42)	0.641
DDI	-6.03	-1.66	4.36 (-6.34 to 15.07)	0.422
			12 months change score	
MOS SF-36 MCS	**6.33**	**7.67**	1.34 (-2.63 to 5.32)	0.505
MOS SF-36 PCS	**7.32**	**10.13**	2.81 (-0.59 to 6.21)	0.104
HUI-3	**0.059**	**0.108**	0.049 (-0.012 to 0.110)	0.112
EuroQoL-5	**0.078**	**0.101**	0.023 (-0.036 to 0.082)	0.446
UDI	**-17.16**	**-17.88**	-0.72 (-9.74 to 8.30)	0.875
IIQ*[1]	-4.76	-4.85	-0.09 (-18.12 to 17.94)	0.992
DDI	-5.90	-4.99	0.91 (-6.55 to 8.36)	0.810
			18 months change score	
MOS SF-36 MCS	**7.01**	**7.09**	0.078 (-3.93 to 4.09)	0.969
MOS SF-36 PCS	**7.94**	**10.45**	2.51 (-0.76 to 5.79)	0.131
HUI-3	**0.064**	**0.114**	0.051 (-0.016 to 0.118)	0.132
EuroQoL-5	**0.085**	**0.109**	0.024 (-0.035 to 0.084)	0.417
UDI	**-17.64**	**-18.59**	-0.94 (-10.46 to 8.58)	0.845
IIQ*[1]	**-10.00**	-9.52	0.47 (-14.10 to 15.05)	0.945
DDI	**-11.29**	-5.45	5.84 (-4.24 to 15.93)	0.254
			24 months change score	
MOS SF-36 MCS	**5.80**	**7.26**	1.47 (-2.78 to 5.71)	0.496
MOS SF-36 PCS	**9.42**	**9.32**	-0.096 (-2.98 to 2.79)	0.948
HUI-3	**0.068**	**0.094**	0.026 (-0.043 to 0.095)	0.462
EuroQoL-5	**0.086**	**0.102**	0.016 (-0.046 to 0.077)	0.620
UDI	**-17.03**	**-14.66**	2.37 (-8.13 to 12.87)	0.656
IIQ*[1]	-7.14	1.59	8.73 (-6.01 to 23.47)	0.226
DDI	**-14.42**	-5.39	9.03 (-0.82 to 18.88)	0.072

MOS: Medical Outcome Study; SF: Short Form; MCS: Mental Component Summary; PCS: Physical Component Summary; HUI-3: Health Utilities Index Mark 3 (HUI-3); EuroQoL-5: EuroQOL 5 dimension 3 level version; UDI: Urogenital Distress Inventory; IIQ: Incontinence Impact Questionnaire; DDI: Defecation Distress Inventory. *[1]IIQ was only filled out by patients who had incontinence problems at that time. Numbers in **bold** indicate a statistically significant ($p<0.05$) change from baseline in the within group analysis

FIGURE 3 A,B. QOL subgroup analysis: UAE failures versus non-failures



Physical health was worse for patients that required a secondary hysterectomy during follow up. This was not the case for mental health, o = UAE, no cross-over, ● = UAE to hysterectomy cross-over

differed significantly (p=0.020 and p=0.015 respectively). At 24 months there was no difference between the groups (MCS: p=0.82; PCS: p=0.92).

Urinary function and defecation

Improvements in urinary function (UDI) occurred mainly during the first 6 months after treatment in both groups (Figure 2E). After 6 months, the UDI scores stabilized in both groups. The defecation function (DDI) continued to improve in the UAE group during the entire study period (Figure 2F). (The IIQ score is not shown graphically because of the small numbers of women who reported incontinence symptoms.) At baseline there was no difference in UDI/IIQ/DDI scores between the groups. Urinary function (UDI) improved significantly compared to baseline up to 6 months after treatment (Table 2). After 6 months the scores stabilized at a continuously higher level compared to baseline. The defecation distress inventory (DDI) score continued to improve significantly only in the UAE group after 12 months follow up.

TABLE 3. Changes in self-reported quality of urinary (A) and defecation (B) function up to 2 years after UAE and hysterectomy compared to baseline

	6 weeks compared to baseline			6 months compared to baseline		
	UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value
Worse	12	10	0.944	8	6	0.901
The same	35	33		36	32	
Better	33	28		34	33	

A. Urinary function

	6 weeks compared to baseline			6 months compared to baseline		
	UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value
Worse	14	21	0.174	8	7	0.999
The same	42	29		43	38	
Better	23	19		26	23	

B. Defecation function

IIQ scores only apply to patients with incontinence at baseline and to those women reporting these complaints during follow up (Table 2). Urinary incontinence was present at baseline in 15/81 (18.5%) UAE patients versus 11/75 (14.7%) hysterectomy patients (p=0.52). At 24 months, 8/15 (53.3%) UAE patients with incontinence at baseline still had urinary incontinence, compared to 9/11 (81.8%) hysterectomy patients (RR: 0.65; 95%CI: 0.38-1.13; p=0.22). In the UAE group 5/66 (6.2%) patients and 7/64 (9.3%) patients in the hysterectomy group without urinary incontinence at baseline reported incontinence at 24 months (RR: 0.69; 95%CI: 0.23-2.07; p=0.51). The IIQ only significantly improved compared to baseline in the UAE group at 18 months follow up (p=0.04). Longitudinal differences between groups were absent. The subgroup analysis, excluding the 19 UAE to hysterectomy crossovers, did not change this result (data not shown).

Changes in self-reported quality of urinary and stool function compared to baseline values (Table 3) showed that at 24 months the majority of patients in both groups reported a similar or improved quality of urinary or stool function compared to baseline (UAE: 85.3% and 91.0%; hysterectomy: 87.5% and 82.9% for urinary and stool function respectively). No significant differences between groups were found.

The use of laxatives decreased over time in the UAE group only: from 9.7% at baseline to 1.3% at 24 months (Table 4). In the hysterectomy group this proportion was stable at 5.8%. In both groups laxative use peaked at 6 weeks: hysterectomy patients used significantly more laxatives than UAE patients, which were the only significant difference between the groups (p=0.01). At baseline 6/80 (7.5%) of UAE patients compared to 6/74 (8.1%) of hysterectomy patients used pads for urinary incontinence. At 24 months 10/80 (12.5%) of UAE patients used incontinence pads compared to 6/73 (8.2%) hysterectomy patients. Of these 5/80 (6.3%) and 2/74 (2.7%) used incontinence pads at both baseline and 24 months follow up.

12 months compared to baseline			24 months compared to baseline		
UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value
11	6	0.120	11	9	0.896
39	28		33	34	
27	36		31	29	

12 months compared to baseline			24 months compared to baseline		
UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value
13	5	0.181	7	12	0.316
35	38		40	31	
28	25		31	27	

TABLE 4. The use of incontinence material and medication to facilitate defecation

Incontinence pads used?	Baseline			6 weeks		
	UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value
yes	6	6	0.89	5	5	0.86
no	74	68		75	67	

A. Urinary incontinence

Lactulants used?	Baseline			6 weeks		
	UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value
yes	7	4	0.54	9	20	0.01
no	72	69		71	52	

B. Constipation

TABLE 5. Satisfaction up to 2 years after UAE and hysterectomy

	6 weeks			6 months		
	UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value
Very satisfied	23	33	0.040	29	42	0.044
Satisfied	19	21		18	15	
Moderately satisfied	20	9		18	6	
Not satisfied or unsatisfied	14	5		7	2	
Moderately unsatisfied	1	0		3	2	
Unsatisfied	1	1		2	1	
Very unsatisfied	3	1		1	1	

Satisfaction

At 24 months (Table 5), most patients in both groups were at least moderately satisfied (UAE 92.5% versus hysterectomy 90.4%). At 24 months hysterectomy patients were overall significantly more satisfied than UAE patients (p=0.02). Logistic regression analysis showed improvement in SF-36 MCS scores to be significantly associated with overall satisfaction (p=0.001) while improvement in PCS was not (p=0.19).

DISCUSSION

Our study demonstrates that both UAE and hysterectomy improve HRQOL significantly in women with symptomatic uterine fibroids. The main increase in HRQOL occurred in the first months after treatment and remained stable thereafter for the average patient. Differences in HRQOL between treatment strategies were only observed in the SF-36 PCS 6 weeks after treatment in favor of UAE, with no further differences between the two treatments at

6 months			24 months		
UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value
7	4	0.54	10	6	0.39
71	68		70	67	

6 months			24 months		
UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value
2	4	0.43	1	4	0.19
75	67		79	69	

12 months			18 months			24 months		
UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value
29	48	0.001	33	43	0.184	34	45	0.020
21	14		19	15		29	16	
18	3		13	6		11	5	
5	3		10	4		2	3	
3	1		2	1		3	0	
1	1		1	1		1	1	
1	0		0	0		0	3	

two years follow up. Except for being employed at baseline, as a predictor for enhanced PCS improvement, no other baseline variables could be identified that predicted HRQOL outcome. Patients undergoing a subsequent hysterectomy after UAE showed significantly lower SF-36 PCS scores in the longitudinal analysis. Evident differences in urinary incontinence related problems were not observed during the two year follow-up period. Defecation related complaints improved only in the UAE group. The only significant difference between the groups at 24 months was the fact that hysterectomy patients were more satisfied with the received treatment than those women treated by UAE.

Patients awaiting hysterectomy are well known to have lower HRQOL scores compared to healthy controls [23]. Improvement of HRQOL after hysterectomy has been described previously [12;23-25]. Also UAE has been shown to improve HRQOL in uncontrolled series [26;27]. One non-randomized trial compared HRQOL between cohorts of women undergoing UAE and hysterectomy using the SF-12 questionnaire. Both treatment groups improved significantly compared to baseline, while no differences were found between both cohorts [28]. Since this was a non-randomized study with significantly lower baseline SF-12 MCS values in

the hysterectomy group, these results are non-informative in that the difference in mental health at baseline confounds these results. This underlines the importance of randomized clinical trials as being the ideal standard for a comparison between treatments. Furthermore these earlier findings suggest UAE patients -at least in some case series- to have less severe complaints than those patients undergoing hysterectomy. This questions the statement 'UAE: an alternative to surgery' as propagated in those reports, because that claim was not substantiated by the actual findings [4;29;30]. Recently the results of another randomized trial comparing UAE with the best surgical option (i.e. hysterectomy or myomectomy) were published [31]. The 'REST trial' demonstrated, like us, that HRQOL at 12 months after treatment did not differ between the groups. Also after longer follow up, like we did, HRQOL does not differ. The similar results of both trials provide profound evidence for comparable HRQOL after UAE and hysterectomy.

At 24 months, a large proportion of patients appreciated their urinary and defecation function as being improved compared to baseline. This is possibly explained by the absence of lower abdominal pressure from the enlarged uterus: after hysterectomy for obvious reasons and after UAE by the impressive volume reduction by an average of 48.2% in our trial [10].

Our high satisfaction rates have been confirmed earlier, both for hysterectomy and UAE, albeit established by different methods [3;6;32-35]. Improvement in SF-36 MCS was associated with higher satisfaction, while improvement in PCS was not. Apparently increased emotional well-being correlates better with satisfaction than increased physical well-being. Hysterectomy patients were more satisfied than UAE patients. It should be noted, however, that this difference mainly resulted from a smaller proportion of UAE patients being 'very satisfied', not because they were 'unsatisfied'.

Some limitations to our study need to be addressed.

The sample size of our study was based on the primary endpoint (i.e. <25% secondary hysterectomies after UAE at two years follow up) and not on HRQOL. However, based on the included number of patients our post-hoc power analysis demonstrated that we had 93% power to demonstrate the true difference in PCS between groups not to exceed 5 points. Since this indeed was the case for the physical health scores, it seems most likely that our findings truly represent equivalence in physical HRQOL between UAE and hysterectomy at two years of follow-up. For MCS the power was 76%. Therefore, equivalence for mental health is somewhat less profound than for physical health.

Furthermore, the SF-36 survey is a thoroughly validated questionnaire measuring general health status, but it is not disease specific for patients with menorrhagia as their predominant clinical problem, since it does not account for the cyclicality of symptoms [36]. Validated and methodologically sound disease-specific HRQOL instruments for specific use in menorrhagia

patients still need to be developed and indeed would be most welcome in the particular patient group under study [36]. A fibroid specific questionnaire has recently been developed [37]. Unfortunately, we were unable to use this questionnaire since it was not yet available when our trial was designed. On the other hand, because fibroids with associated symptoms are being removed in hysterectomy patients, a comparison between the hysterectomy and the UAE group would probably be hampered by asymmetrical outcome measures when using fibroid/menorrhagia specific questionnaires. We therefore believe that general HRQOL scores are presently the most appropriate instruments for the comparison described in this study.

In a previous report we demonstrated UAE to be a good alternative to hysterectomy in the treatment of uterine fibroids, unless patients seek a definite solution for their bleeding problems [10]. Except for a small short-term advantage in favor of UAE, the present analysis of HRQOL outcomes does not alter our earlier conclusion. Our findings confirm UAE to be a valuable alternative to hysterectomy also in terms of quality of life. Since the results for all HRQOL instruments are virtually identical between 6 and 24 months after treatment, it seems unlikely that any differences will become apparent after this period, suggesting enduring increment in quality of life after both treatments. However, when new fibroids develop, which might occur especially in younger patients, HRQOL might decrease in the UAE group. Future research will need to elucidate this subject.

In summary, both UAE and hysterectomy improved HRQOL significantly. No differences were observed between both groups in terms of HRQOL at 24 months follow-up. Patients' satisfaction, however, was somewhat higher after hysterectomy than after UAE. Based on HRQOL results UAE is a good alternative to hysterectomy.

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9

SEXUALITY AND BODY IMAGE AFTER UTERINE ARTERY EMBOLIZATION AND HYSTERECTOMY IN THE TREATMENT OF UTERINE FIBROIDS: A RANDOMIZED COMPARISON

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ABSTRACT

Objective

To investigate the effect of uterine artery embolization (UAE) on sexual functioning and body image in a randomized comparison to hysterectomy for symptomatic uterine fibroids.

Methods

The EMbolization versus hysterectoMY (EMMY) trial is a randomized controlled study, conducted in 28 Dutch hospitals. Patients were allocated UAE (n=88) or hysterectomy (n=89). The Sexual Activity Questionnaire (SAQ) and the Body Image Scale (BIS) were completed by all patients at baseline and 6 weeks and 6, 12, 18, 24 months after treatment.

Results

Repeated measurements on SAQ-scores revealed no differences between both groups. Sexual functioning [SAQ] improved both after UAE and hysterectomy, but improvement was only significant in UAE patients for the dimensions discomfort and habit. Overall quality of sexual life deteriorated in a minority of cases at all time points, with no significant differences between the groups (at 24 months: UAE: 29.3% versus hysterectomy: 23.5%; p=0.32). At 24 months BIS-score had improved in both groups compared to baseline, but the change was only significant in the UAE group (p=0.009). Between the groups no significant difference was observed for the BIS-scores.

Conclusion

At 24 months no differences in sexuality and body image were observed between UAE and hysterectomy. On average, both after UAE and hysterectomy sexual functioning and body image scores improved, but only significantly so after UAE.

INTRODUCTION

When hysterectomy looms as a definite treatment for fibroid related menorrhagia, women often express their concern about negative effects of the operation on their sexual wellbeing [1]. Since the uterus is an intrinsic element of sexual image and an essential attribute of femininity, hysterectomy may also interfere with the woman's body image [2]. For some women, these concerns are one of the reasons to choose alternative treatment options. During the last decade, uterine artery embolization (UAE) has emerged as an alternative treatment for hysterectomy [3]. Although UAE has been investigated in several case series and one small pre-consent randomized trial, the advantage of UAE in terms of sexual wellbeing and body image in comparison to hysterectomy remains unknown, since randomized controlled trials on this subject are not available as yet [4-8]. We initiated a randomized trial comparing UAE and hysterectomy and have published several short term results previously [9-11]. In the present paper, we compare changes in sexuality and body image in patients with symptomatic uterine fibroids who were randomly assigned to either UAE or hysterectomy.

METHODS

STUDY DESIGN

The details of our study design have been described elsewhere and will be discussed here briefly [9].

The EMMY trial (EMbolization versus hysterectoMY) is a prospective randomized multi centre clinical trial with 28 participating hospitals. Eligible patients met the following inclusion criteria: they were clinically diagnosed with uterine fibroids (confirmed by ultrasonography), had menorrhagia as major complaint, were pre-menopausal, were to be scheduled for a hysterectomy as the final solution for their clinical problems and had no wish to conceive.

Eligible patients were informed verbally and in writing about possible risks and benefits of both procedures, and invited to participate in the trial. After written informed consent had been obtained, patients were randomly assigned (1:1) to UAE or hysterectomy by computerized randomization, stratified for hospital. The study was approved by the Dutch Central Committee Involving Human Subjects (www.ccmo.nl) and the local ethics committees of all participating hospitals.

PRE-ASSESSMENT

All patients were assessed by the attending gynecologist. Current symptoms and a complete medical and gynecological history were recorded. All patients underwent a pelvic ultrasound to determine the number of fibroids and the size of the largest fibroid. Socio-demographic characteristics were assessed by means of a questionnaire.

PROCEDURES

Uterine artery embolization

UAE was performed by an interventional radiologist. A catheter was introduced into the femoral artery and advanced over the aortic bifurcation to the contra-lateral internal iliac artery, and digital subtraction angiography was performed to identify the origin of the uterine artery. When catheters were placed correctly, the UAE was carried out. Polyvinyl alcohol particles (PVA) with a size of 355-500 μm were used in all procedures. UAE patients were advised to refrain from sexual intercourse for at least two weeks and thereafter depending on their complaints.

Hysterectomy

The type of hysterectomy and the route of access were determined by the gynecologist. The following procedures were allowed: abdominal hysterectomy, vaginal hysterectomy, laparoscopically assisted vaginal hysterectomy and laparoscopic hysterectomy. Both supravaginal and total hysterectomies were allowed. After discharge hysterectomy patients were advised not to have sex until the first outpatient visit at 6 weeks.

QUESTIONNAIRES

Sexual functioning and body image were assessed by means of self-report questionnaires. At baseline, questionnaires were completed by all patients before randomization. Follow-up questionnaires were completed at 6 weeks and 6, 12, 18, 24 months after treatment. The questionnaire consisted of the Sexual Activity Questionnaire (SAQ), the Body Image Scale (BIS) and the Mental Component Summary (MCS, as part of the Medical Outcome Study Short Form (MOS SF-36)).

The SAQ, originally designed to investigate sexual functioning in women treated with tamoxifen because of a positive family history of breast cancer [12], is useful also in women with non-malignant gynecological disorders [13]. In Table 1 the SAQ is displayed. The questionnaire consists of three dimensions, each dimension yields its own score: pleasure from sexual intercourse (desire, enjoyment and satisfaction; score range: 0-18), discomfort during intercourse (score range: 0-6), and habit (frequency; score range 0-3). Pleasure and

TABLE 1. The sexual activity questionnaire (SAQ) and the body image scale (BIS)

SEXUAL ACTIVITY QUESTIONNAIRE
Dimension pleasure:
1. Was having sex an important part of your life in the last month?
2. Did you enjoy sexual activity in the last month?
3. Did you desire to have sex with your partner in the last month?
4. In general were you satisfied after sexual activity in the last month?
5. How often did you engage in sexual activity in the last month?
6. Were you satisfied with the frequency of sex in the last month?
Dimension discomfort
1. Did you notice dryness of your vagina in the last month?
2. Did you feel pain or discomfort in the last month?
Dimension habit
1. How did the frequency of sexual behavior in the last month compare with what is usual for you?
BODY IMAGE SCALE
In the last month:
1. Have you been feeling self-conscious about your appearance?
2. (Have you felt less physically attractive as a result of your menstrual bleeding problem?)
3. Have you been dissatisfied with the appearance when dressed?
4. (Have you been feeling less feminine as a result of your menstrual bleeding problem?)
5. Did you find it difficult to look at yourself naked?
6. (Have you been feeling less sexually attractive as a result of your menstrual bleeding problem?)
7. Did you avoid people because of the way you felt about your appearance?
8. Have you been feeling the treatment has left your body less whole?
9. Have you felt dissatisfied with your body?
10. Have you been dissatisfied with the appearance of your scar?

The questions of the BIS displayed in parentheses have been omitted

habit are good with higher scores, while discomfort is worse with higher scores. The SAQ was only filled out by patients that were sexually active the month before they received the questionnaire.

Furthermore, participating patients were asked to judge their current sexual life in two questions: 'How would you describe the quality of your current sexual life?' and 'How well can you live with your current sexual life?' One of the following responses could be ticked: 'very good', 'good', 'moderately good', 'good nor bad', 'moderately bad', 'bad' and 'very bad'.

The Body Image Scale (BIS) was designed in order to asses changes in body image among cancer patients [14]. The questionnaire was also found reliable and valid in women with benign gynecological conditions [15]. Table 1 displays the questions of which the BIS consists. Unfortunately, questions #2, #4 and #6 were not represented correctly in the questionnaire due to a translation error. Therefore we decided to omit these questions in order to attain a comparable outcome between groups. The BIS score ranges from 0-30. A higher BIS score indicates a worse body image.

In order to assess mental health before treatment as a predictor of worse sexual function after treatment, the Mental Component Summary score of the 36-item Medical Outcome Study Short Form 36 (MOS SF-36 MCS) was used [16]. This was done because a bad preoperative mental health is associated with bad sexual life outcome [17].

STATISTICAL ANALYSIS

Data entry was performed using SPSS data entry for Windows 3.0. A random sample of 10% of the questionnaires was visually double checked by an independent second investigator revealing a false entry level of 0.3%. All false data entries were corrected.

All analyses were performed using SPSS (release 11.5.1) statistical software. Missing items in the questionnaire were treated as follows. For the SAQ no advice is available on scoring missing items. If one item was missing, we regarded the dimension score (which the item was part of) as being missing completely, according to earlier research [18]. For the BIS no missing values were allowed since three questions were omitted already. In these cases, the entire score was omitted. For the three omitted questions, the individual mean score of the remaining 7 questions was imputed.

We first determined how many patients in both treatment groups were sexually active before and after treatment. An overall percentage per treatment group was calculated after which sexual activity in subgroups was assessed: those being sexually active and those *not* being sexually active before treatment. Secondly, the mean of the dimension scores were plotted for the hysterectomy and UAE group. Thirdly, the mean differences between all follow up SAQ dimension scores and baseline were compared between treatment groups. This was only possible for patients who were sexually active both before and after treatment. Within group changes were analyzed as well. Similar analyses were performed for the BIS. Differences in pleasure, discomfort, habit (SAQ) and body image (BIS) between groups over time were tested with repeated measurement analysis, excluding the 6 weeks measurement for the SAQ, since a high proportion of patients were expected not to be sexually active at that time and therefore not to yield a score. Differences in continuous variables were tested with Student's t-test. Differences in data with skewed distributions were tested with the non-parametric Mann-Whitney-U test.

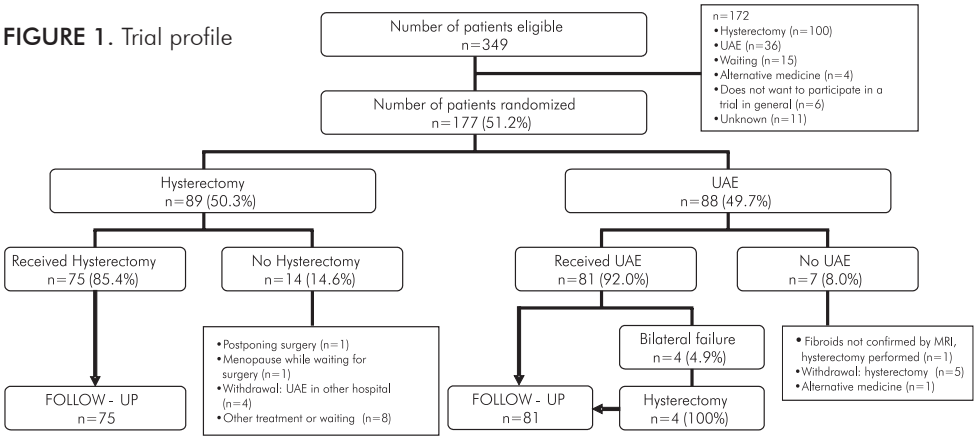
The two added questions on the quality of current sexual life were compared between the groups using the Chi square test (or Fishers' Exact test when appropriate). Furthermore, the quality of sex-life and the additional questions at the various follow-up moments were compared to baseline, yielding three different options: 'worse', 'the same' or 'better' compared to baseline. Differences between the groups were compared with the Chi square test (or Fishers' Exact test when appropriate).

Logistic regression analysis was performed to investigate variables associated with a worse sexual life quality at 24 months after treatment compared to baseline versus unchanged or improved quality of sexual life. Firstly, univariate analysis was performed with the following baseline characteristics: intended treatment, age, BMI, parity, ethnicity, having a partner, employment status, smoking status, number of fibroids, uterine volume measured by ultrasound, dominant fibroid volume measured by ultrasound, the existence of any co-morbid disease and mental health status (MOS SF-36 MCS) at baseline. Secondly, covariates with p-values <0.1 in the univariate analysis were selected for multiple regression analysis.
All analyses were two-tailed and carried out based on the intention to treat principle. A p-value <0.05 (two-tailed) was considered statistically significant.

RESULTS

Patients were enrolled between March 2002 and February 2004. Of 349 eligible patients, 177 were randomized: 89 were allocated hysterectomy and 88 were allocated UAE. In the hysterectomy group 14 patients refused the allocated treatment compared to 7 patients

FIGURE 1. Trial profile



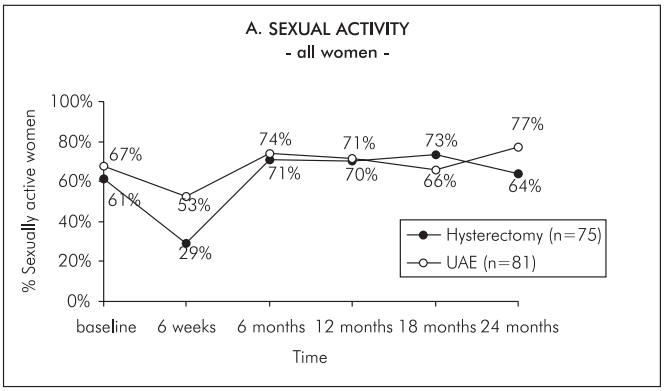
in the UAE group, and these patients withdrew from participation. In 4 UAE patients embolization failed bilaterally. These patients subsequently had a hysterectomy, but were analyzed in the UAE group according to the intention to treat principle (Figure 1) [9]. The baseline characteristics of all randomized patients are described in Table 2. No differences between the groups are apparent, as expected considering the randomized design.

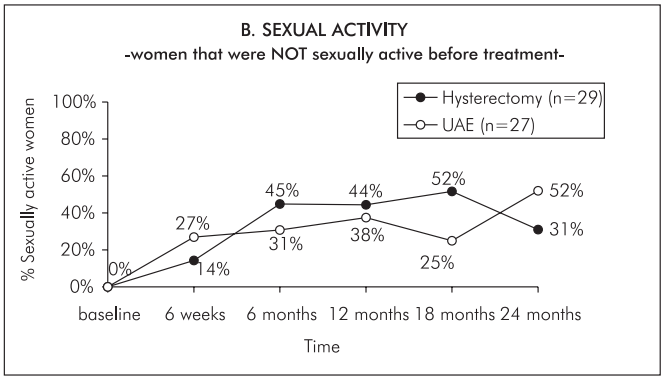
TABLE 2. Baseline characteristics

	UAE n=88 n (%)	Hysterectomy n=89 n (%)
Age (years)		
mean (SD)	44.6 (4.8)	45.4 (4.2)
Body Mass Index (weight (kg) / length $(m)^2$)		
mean (SD)	26.7 (5.6)	25.4 (4.0)
Parity		
0	30 (34.1)	20 (22.5)
1 or more	58 (65.9)	69 (77.5)
Ethnicity		
Black	24 (27.3)	20 (22.5)
White	54 (61.4)	57 (64.0)
Other	10 (11.4)	12 (13.5)
Marital status		
Single	16 (18.2)	13 (14.8)
Married	55 (62.5)	54 (61.4)
Living Apart Together	5 (5.7)	4 (4.5)
Divorced	12 (13.6)	15 (17.0)
Widow	0 (0)	2 (2.3)
Partner relationship		
No partner	13 (15.3)	19 (22.4)
Partner	72 (84.7)	66 (77.6)
Employment status		
Employed	68 (77.3)	69 (78.4)
Unemployed	20 (22.7)	19 (21.6)
Smoking status		
Current smoker	21 (23.9)	23 (25.8)
Former smoker	11 (12.5)	14 (15.7)
Non-smoker	56 (63.6)	52 (58.4)
Comorbid disease*[1]		
Any comorbid disease	24 (27.3)	22 (24.7)
Number of fibroids		
Median (range)	2 (1-20)	2 (1-9)
Uterine volume (cm^3)		
Median (range)	321 (31-3005)	313 (58-3617)
Fibroid volume (dominant fibroid, cm^3)		
Median (range)	59 (1-673)	87 (4-1641)
Mental Component Summary (SF-36)		
Mean (SD)	40.9 (10.7)	41.5 (11.0)

*[1] Any of the following: hypertension, diabetes, astma, clotting disease, system-disease or other

The number of questionnaires available for analysis ranged from 96.0% (baseline) to 98.7% (6 weeks, 24 months). Before treatment 54/81 (67%) and 46/75 (61%) of the participating patients were sexually active in the UAE and hysterectomy group respectively (Figure 2). Six weeks after treatment, sexual activity had decreased in both groups, with significantly more patients showing sexual activity in the UAE group compared to hysterectomy (53%





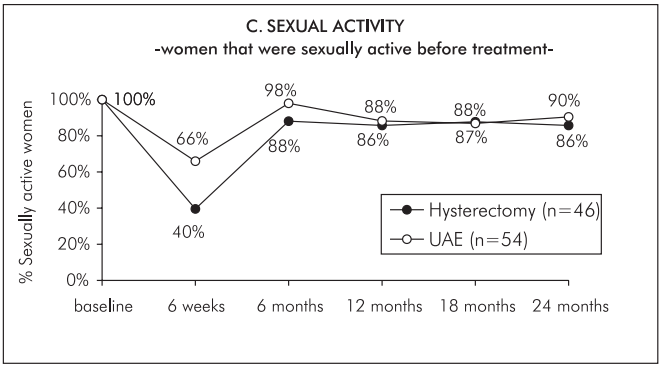


FIGURE 2A-C. Proportion of sexually active women by treatment strategy, over time. A is the weighted average of women who were not sexually active at baseline (B) and those that were sexually active at baseline (C)

versus 29%; p=0.004). Hereafter sexual activity restored in both groups with no significant differences between the groups at 24 months (p=0.07).

Patients who were not sexually active before treatment gradually resumed sexual activities after both UAE and hysterectomy (Figure 2B). After 24 months 31% (hysterectomy) and 52% (UAE) were sexually active (p=0.118). No significant differences were observed between the groups.

Among those patients who were sexually active before treatment, there was a major drop in activity at 6 weeks after treatment which restored partially. After two years, 86% (UAE) and

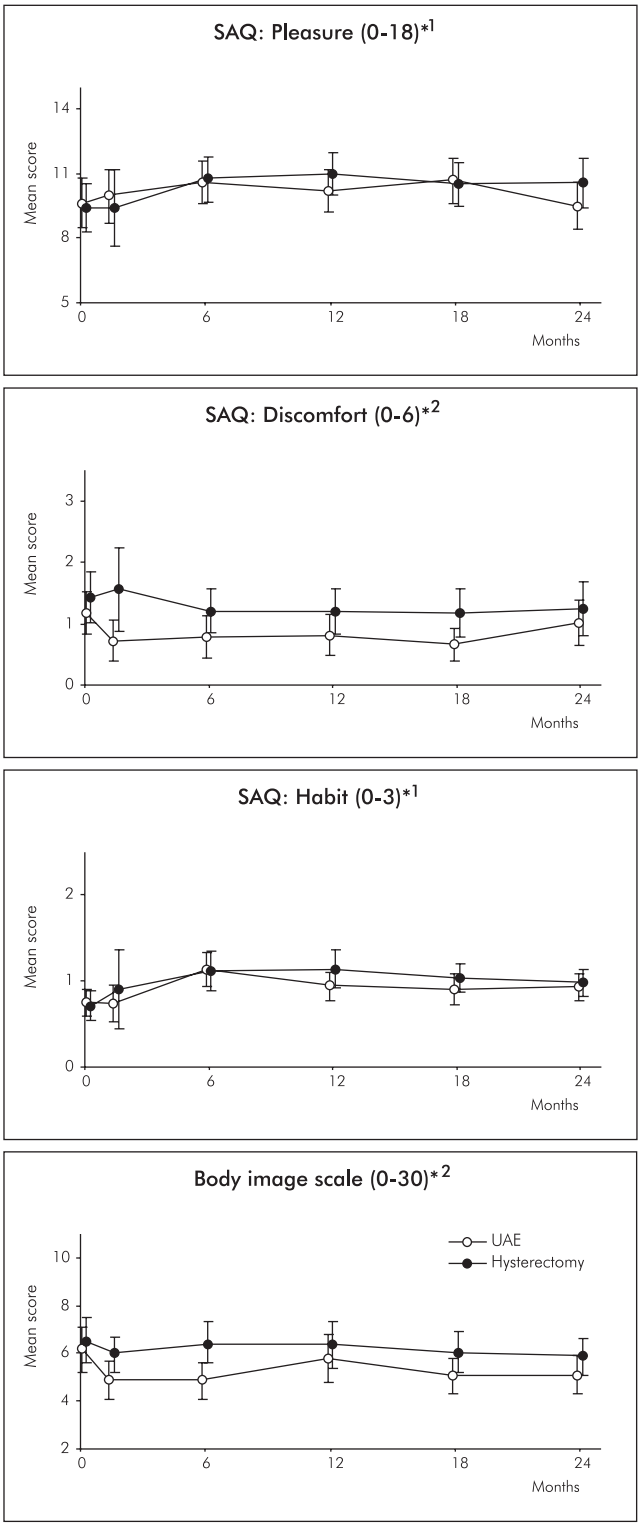


FIGURE 3. Pleasure, discomfort, habit and body image by treatment strategy, over time

*1 A higher score represents more favorable sexual functioning (pleasure, habit); *2 A lower score represents more favorable sexual functioning (discomfort) or body image

90% (hysterectomy) of these patients had resumed their sexual activities (Figure 2C). Only at six weeks significantly more UAE patients had resumed sexual activity (p=0.01).

Figure 3 shows the course of pleasure, discomfort and habit (SAQ) and body image (BIS) scores over time. There were no differences between the groups at baseline (pleasure: p=0.76; discomfort: p=0.44; habit: p=0.77; body image: p=0.60). Repeated measurements revealed no differences between the groups for pleasure (p=0.343), discomfort (p=0.246), habit (p=0.453) and body image (p=0.359). Table 3 shows the changes in dimension scores per treatment group for patients that were sexually active at baseline. Positive numbers for pleasure and habit and negative numbers for discomfort and body image are indicative for improvement compared to baseline. No significant differences were found between the two treatment groups at all time points, except for body image at 6 months after treatment: body image had improved significantly more in UAE patients than in hysterectomy patients

TABLE 3. Mean differences in pleasure, discomfort, habit and body image compared to baseline, by treatment strategy, over time

	UAE Mean difference from baseline	Hysterectomy Mean difference from baseline	Δmean (95%CI)	p-value
SAQ: Pleasure (0-18)*[1]				
6 weeks	0.29	-0.50	0.79 (-1.39 to 2.98)	0.47
6 months	**1.63**	**1.23**	0.40 (-1.14 to 1.93)	0.61
12 months	0.95	**1.49**	-0.53 (-2.08 to 1.02)	0.50
18 months	**1.86**	0.68	1.18 (-0.34 to 2.71)	0.13
24 months	0.89	1.18	0.74 (-2.01 to 1.43)	0.74
SAQ: Discomfort (0-6)*[2]				
6 weeks	-0.25	-0.21	-0.04 (-1.35 to 1.28)	0.96
6 months	**-0.58**	-0.32	-0.26 (-0.88 to 0.37)	0.41
12 months	**-0.47**	-0.47	0.01 (-0.60 to 0.61)	0.98
18 months	**-0.51**	-0.29	-0.51 (-0.86 to 0.43)	0.51
24 months	**-0.43**	-0.49	0.05 (-0.66 to 0.77)	0.88
SAQ: Habit (0-3)*[1]				
6 weeks	-0.03	0.00	-0.03 (-0.59 to 0.53)	0.92
6 months	**0.48**	0.28	0.20 (-0.18 to 0.59)	0.30
12 months	0.18	**0.42**	-0.24 (-0.64 to 0.16)	0.24
18 months	**0.27**	0.19	0.07 (-0.30 to 0.44)	0.70
24 months	**0.28**	0.22	0.06 (-0.30 to 0.43)	0.74
BIS (0-30)*[2]				
6 weeks	**-1.27**	-0.28	-1.00 (-2.19 to 0.19)	0.10
6 months	**-1.34**	0.00	-1.34 (-2.50 to -0.18)	0.02
12 months	-0.24	0.08	0.31 (-1.62 to 0.99)	0.64
18 months	**-1.24**	-0.28	-0.96 (-2.27 to 0.36)	0.15
24 months	**-1.06**	-0.50	-0.56 (-1.76 to 0.65)	0.36

Bold numbers indicate a significant difference from baseline within group (p<0.05)

*[1] A higher score represents more favorable sexual functioning (pleasure, habit);

*[2] A lower score represents more favorable sexual functioning (discomfort) or body image

TABLE 4. Satisfaction with sexual life and ability to cope with sexual life by treatment strategy, over time

How is the quality of your current sex-life?	Baseline		
	UAE (n=81)	Hyst. (n=75)	p-value
Very good	15	8	0.84
Good	22	27	
Somewhat good	15	13	
Not good, nor bad	12	12	
Somewhat bad	6	6	
Bad	4	3	
Very bad	3	3	
How well can you live with your current sex-life?	Baseline		
	UAE (n=81)	Hyst. (n=75)	p-value
Very good	9	3	0.77
Good	20	21	
Somewhat good	10	12	
Not good, nor bad	20	17	
Somewhat bad	8	9	
Bad	4	4	
Very bad	6	5	

(UAE: -1.34 versus hysterectomy: no change; p=0.02). Within the groups however, a significant improvement of various dimension scores was noted (indicated in bold): at 24 months UAE patients reported significantly less discomfort, more habit and a better body image compared to baseline (p=0.022, p=0.022, p=0.009 respectively). At 24 months hysterectomy patients improved on all dimensions compared to baseline, but differences were not statistically significant.

Table 4 describes the patients' quality of their sex-life at 6 weeks and 12, 24 months. No differences between groups were observed. Table 5 depicts the proportion of patients who judged the quality of sexual life as better, comparable, or worse compared to baseline based on the question: 'How is the quality of your current sexual life?' A minority of patients reported worsened sexual life quality compared to baseline at all time points. At 24 months the proportion of patients reporting a worse sexual life compared to baseline was slightly higher in the UAE than in the hysterectomy group, but not statistically significant (29.3% versus 23.5%; p=0.43).

Univariate logistic regression analysis revealed BMI, number of fibroids and the presence of co-morbid disease to be associated with a worsened quality of sexual life at 24 months compared to baseline ($p<0.1$). Allocated treatment and mental health at baseline were not associated with worse outcome.

6 weeks			12 months			24 months		
UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value
7	1	0.48	7	11	0.35	8	11	0.54
25	22		31	18		29	21	
12	13		9	11		8	12	
23	19		15	21		16	15	
4	4		5	3		8	8	
5	8		3	4		4	4	
2	1		4	2		5	1	
6 weeks			12 months			24 months		
UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value	UAE (n=81)	Hyst. (n=75)	p-value
11	6	0.33	18	17	0.93	20	17	0.78
37	30		35	30		34	31	
15	16		11	13		10	11	
10	5		6	4		10	6	
2	5		1	3		2	5	
2	5		2	2		2	2	
0	1		1	1		0	0	

TABLE 5. Changes in sexual wellbeing compared to baseline by treatment strategy, over time

	UAE n=81	Hysterectomy n=75	p-value
6 weeks			
Worse	22	20	0.95
The same	30	24	
Improved	24	21	
6 months			
Worse	16	13	0.68
The same	25	27	
Improved	32	25	
12 months			
Worse	17	14	0.81
The same	29	26	
Improved	25	27	
18 months			
Worse	22	11	0.15
The same	20	25	
Improved	31	29	
24 months			
Worse	22	16	0.32
The same	27	20	
Improved	26	32	

BMI was not significant in the multiple regression analysis (p=0.163). The other three parameters remained significantly associated with worse outcome: a higher number of fibroids (OR: 0.69; 95%CI: 0.51-0.94; p=0.018) predicted a decreased risk of having worse sexual life at 24 months compared to baseline, while the presence of co-morbid disease (OR: 3.20; 95%CI: 1.38-7.41; p=0.007) was associated with an increased risk of a worse sexual life quality at 24 months after treatment compared to baseline.

DISCUSSION

In our trial no differences on average in sexual function at 24 months were observed between UAE and hysterectomy. After both treatments pleasure and habit improved and discomfort decreased at 24 months compared to baseline, although only the UAE group showed significant improvement in discomfort and habit.

The improvement of most aspects of sexual functioning after UAE was in accordance with the scarce literature on sexual functioning after UAE [19]. This study found a significant improvement in sexual function as well. In contrast, sexual functioning after hysterectomy has been a topic of great interest and consequently has received much attention in the literature. Improvement in sexual functioning after hysterectomy might indirectly be associated with the consequences of surgery, such as less worry about unwanted pregnancy, absence of vaginal bleeding and more time for sexual activities by the cessation of monthly periods [20]. Most reports on sexual functioning after hysterectomy found significant benefits in different aspects of sexual functioning, while we found no significant improvement within that group at 24 months of follow up [18;21-26]. The fact that improvement of sexual functioning was not statistically significant in our hysterectomy group might be caused by insufficient power: with larger populations the improvement might have become significant. The lack of power is possibly explained by the decreased sample size for the SAQ scores in our population: change scores were only available from women who were sexually active at baseline. Furthermore, the studies on sexuality after hysterectomy have different follow up intervals ranging from 6 months to 2 years. In our series, hysterectomy patients experienced significantly improved pleasure and habit scores at 12 months follow up. These results might indicate that improvement in sexual functioning after hysterectomy could be temporary. On the other hand, a review article by Maas et al. suggests that there is no scientific proof for either improvement or deterioration of sexual functioning after hysterectomy, unless hysterectomy was performed based on a sound clinical indication [20]. In our patient group, however, there was no doubt about the indication: complaints were seriously and lengthy enough to warrant a hysterectomy.

Although, on average, SAQ scores for the group as a whole improved, there was a small group of women that reported a deterioration in self reported quality of sexual life, consistent with other reports [21-23;25;27]. Deterioration of sexual life is possibly of greater concern to patients than the improvement after treatment. Regression analysis on worsened of sexual life revealed that women with a low number of fibroids (possibly representing a group of women with less severe complaints) and women with other concomitant chronic diseases present might not be helped by these treatments in terms of sexual life improvement.

The improved body image after UAE in our series is in accordance with another study that reports a higher self-consciousness after UAE [19]. After hysterectomy a period of temporary worsened body image following the operation has been described[18;27;28]. This was not confirmed by our results, but in accordance with these studies a normal or even improved body image was found one year after hysterectomy.

There are several limitations of our study that need to be addressed:

First of all, the values of the SAQ-dimensions were based on all sexual active women at the various points in time. Reported values may reflect an ever changing group of sexually active women. At any stage, some women will cease sexual activity, others initiate. Of all non-sexually active women before treatment, 50% became active after treatment. When comparing pre- and post-treatment scores, these women cannot be included, since the baseline score is missing.

Secondly, the significant difference between resumption of sexual activity between the groups at 6 weeks is probably explained by the above mentioned counseling after both treatments: hysterectomy patients in our trial were told not to have sex until the first outpatient visit at 6 weeks, while UAE patients were advised to refrain from intercourse for at least two weeks and thereafter depending on their complaints.

Thirdly, we allowed all kinds of hysterectomies, thereby possibly biasing the results in the hysterectomy group. However, various reports found no long term differences in sexual functioning after various surgical routes of hysterectomy [18;23;26].

Finally, as described above, three questions in the BIS were omitted because of wrongly posed questions, thereby creating asymmetry in the treatment arms. Since the remaining questions in both groups were identical, the comparison between the groups is still valid, but reduces comparability with other series.

In conclusion, at 24 months no differences in sexuality and body image were observed between the UAE and hysterectomy group. Both after UAE and hysterectomy, on average, sexual functioning and body image scores improved, but only significantly so after UAE.

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SUBMITTED

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AN ECONOMIC EVALUATION OF UTERINE ARTERY EMBOLIZATION VERSUS HYSTERECTOMY IN THE TREATMENT OF SYMPTOMATIC UTERINE FIBROIDS: RESULTS FROM THE RANDOMIZED EMMY TRIAL

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ABSTRACT

Purpose

To investigate if uterine artery embolization (UAE) is a cost-effective alternative to hysterectomy for patients with symptomatic uterine fibroids, we performed an economic evaluation alongside the multi-centre randomized EMMY trial.

Methods

Between February 2002 and February 2004 177 patients were randomized to UAE (n=88) or hysterectomy (n=89) and followed until 24 months after initial treatment allocation.
Conditional on the equivalence of clinical outcome, a cost minimization analysis was performed according to the intention to treat principle. Costs included health care costs inside and outside the hospital as well as costs related to absence from work (societal perspective). Cumulative standardized costs were estimated as volumes multiplied with prices. The non-parametric bootstrap method was used to quantify differences in mean (95%CI) costs between the strategies.

Results

In total 81 patients underwent UAE, while 75 underwent hysterectomy. In the UAE group, 19 (23.5%) secondary hysterectomies were performed. The mean total costs per patient in the UAE group were significantly lower than in the hysterectomy group ($11626 vs. $18563; mean difference - $6936 (-37%), 95%CI [- $9548 to - $4281]. The direct medical in-hospital costs were significantly lower in the UAE strategy: $6688 vs. $8313 (mean difference: - $1624 (-20%), 95%CI [- $2605 to - $586]). Direct medical out-of-hospital and direct non-medical costs were low in both groups (mean cost difference: $156 in favor of hysterectomy). The costs related to absence from work differed significantly between the treatment strategies in favor of UAE (mean difference: - $5453, 95%CI [- $7718 to - $3107]). The costs of absence from work accounted for 79% of the difference in total costs.

Conclusion

The 24 months cumulative costs of UAE are lower compared to hysterectomy. From a societal economic perspective, UAE is the superior treatment strategy in women with symptomatic uterine fibroids.

INTRODUCTION

Uterine fibroids are benign tumors arising from smooth muscle cells of the uterine wall. Fibroids are clinically apparent in approximately 25 percent of women of reproductive age and are found in approximately 77 percent of surgically excised uteri on histopathologic examination [1]. Fibroids may cause several symptoms, such as menorrhagia, pain and bulk-related complaints, which may compromise women's health status. For symptomatic uterine fibroids a wide variety of both medical and surgical treatment options are available [1]. Hysterectomy is indicated whenever other treatment options, e.g. pharmaceutical treatment or myomectomy, are either unsuitable or ineffective, and when there is no desire for future pregnancy.

Concerns about the invasiveness of hysterectomy and its treatment related morbidity have prompted the development of various less invasive alternatives. As a consequence uterine artery embolization (UAE) has been proposed as a promising alternative for the treatment of heavy menstrual bleeding since 1995 [2]. Several large case series have indeed suggested UAE to be advantageous over surgery [3-6], but those studies were hampered by the inclusion of patients with strong treatment preferences and the lack of a control group.

From a societal perspective, the preferred treatment strategy is the one that yields favorable health gains relative to associated costs ('value for money'). In order to make a proper comparison in terms of effectiveness and costs-effectiveness, we initiated a prospective, multi-centre, randomized clinical trial comparing UAE with hysterectomy for the treatment of menorrhagia caused by uterine fibroids, the EMMY-trial. Results so far indicate that UAE is a safe procedure, which is able to avoid hysterectomy in 76.5% of cases with no difference in quality of life at 24 months, justifying the conclusion that UAE is a valuable alternative for hysterectomy [7]. This report addresses the question as to whether UAE is a cost-effective alternative to hysterectomy in the treatment of uterine fibroid related menorrhagia, thereby using data from our randomized clinical trial.

METHODS

CLINICAL STUDY DESIGN

The EMMY (Embolization versus hysterectoMY) trial is a multi-centre randomized clinical study comparing UAE with hysterectomy as a treatment for heavy menstrual bleeding caused by uterine fibroids. Twenty-eight hospitals in The Netherlands participated in the trial. The study was approved by the Central Committee Involving Human Subjects (www.ccmo.nl) and

by local ethics committees of participating hospitals. The inclusion and exclusion criteria for trial participation were: 1) the clinical diagnosis of uterine fibroids had been confirmed by ultrasonography; 2) menorrhagia (subjectively reported by the patient as increased or prolonged menstrual blood loss causing dysfunction in daily life) was the predominant complaint; 3) patients were premenopausal; 4) hysterectomy was thought to be the ultimate solution as other treatment options were unsuitable or had failed to provide symptomatic relief; 4) no desire for future pregnancy; 5) absence of the following disorders: renal failure (creatinine >150 mmol/L), active pelvic infection, clotting disorders, allergy to contrast fluid, (suspected) uterine malignancy, submucosal fibroids protruding by >50% within the uterine cavity, or pedunculated abdominal fibroids.

After written consent was obtained by the attending gynecologist and patients had completed an extensive questionnaire, patients were randomly assigned 1:1 to either UAE or hysterectomy using a computer based minimization scheme, stratified for each study centre.

TREATMENT STRATEGIES

Pre-intervention period

Preceding both interventions all patients completed a questionnaire addressing baseline characteristics (health-related quality of life questionnaires, status of menorrhagia symptoms and socio-demographic characteristics). They visited the outpatient gynecology clinic for an extensive case history and physical examination. All patients underwent a pelvic ultrasound examination either trans-vaginally or trans-abdominally as well as various laboratory investigations.

Whenever a patient was allocated UAE, a pelvic MRI was performed. No additional visit with the interventional radiologist was planned. Patients' allocated hysterectomy visited the anesthesiology department preoperatively. In the present economic analysis, these visits and procedures were part of the pre-procedural work up costs.

Uterine artery embolization (UAE)

UAE was performed under local or epidural/spinal anesthesia by an interventional radiologist under supervision of an experienced interventional radiologist (JR) with ample experience in UAE (>50 procedures).We advised the use of the following pain protocol to all participating units during admission: acetaminophen (three doses at 1000 mg) and nonsteroidal anti-inflammatory drugs (diclofenac, three doses at 50 mg), and opiates (morphine 10 mg; a maximum of six times per day) or epidural anesthesia whenever pain control was insufficient. The use of antibiotics was not standardized. A 4- or 5-French catheter was introduced into the femoral artery and advanced over the aortic bifurcation to the contralateral internal iliac

artery. During the procedure digital subtraction angiography was performed to identify the origin of the uterine artery. When catheters were in the correct position, actual embolization was carried out with polyvinyl alcohol particles (355-500 μm) (Contour; Boston Scientific, Maastricht, The Netherlands). Microcatheters were allowed but not used routinely in this study. UAE was considered successful when parenchyma filling of the fibroids had stopped (target embolization) or until the main uterine artery was blocked (selective embolization).
After the procedure, women were admitted to the gynecology ward for further care. All patients were advised to stay in hospital for at least one night.

Hysterectomy

The type of hysterectomy and the route of access were left at the discretion of the attending gynecologist. The following procedures were allowed: abdominal hysterectomy, vaginal hysterectomy, laparoscopic hysterectomy and laparoscopically assisted vaginal hysterectomy. Both supravaginal and total hysterectomies were permitted. We used no uniform standardized guidelines for: antibiotic prophylaxis, type of anesthesia, analgesics during admission and hospital discharge criteria.

Post-intervention period

After the primary interventions, patients were seen at the gynecology outpatient clinic for clinical follow-up. Furthermore, they received a self-report questionnaire by mail (which contained, among others, the Medical Outcome Study Short Form 36 (SF-36) [8], the EuroQOL 5 dimension 3 level version (EuroQol 5) [9], the Health Utilities Index Mark 3 (HUI-3) [10] and an out-of-hospital resource use survey to be filled in at home at 6 weeks and 6, 12, 18 and 24 months. Analyses of survey responses (SF-36, EuroQol 5 and HUI-3) were performed according to accepted scoring algorithms.

ECONOMIC ANALYSIS

Our aim in the present economic evaluation was to provide a decision-analytic framework to support medical decision making as a trade-off between incremental health gains (clinical effectiveness) versus incremental costs in the comparison between UAE and hysterectomy [11].

Effectiveness

Clinical effectiveness was evaluated from the perspective of the QALY-model which combines mortality and morbidity in one outcome measure [12]. In our study no mortalities occurred. Results of the RCT showed UAE to be clinically non-inferior to hysterectomy (i.e. the observed mean difference in clinical effectiveness was less than our predefined cut-off value of 25%),

TABLE 1. Health related quality of life outcome: 24 months change score of the MOS SF-36, the EuroQol-5 and the HUI-3

	UAE (n=81) Mean change score compared to baseline	Hysterectomy (n=75) Mean change score compared to baseline	Mean difference in change score (95%CI)	p-value
MOS SF-36 MCS	5.8	7.26	1.47 (-2.78 to 5.71)	0.5
MOS SF-36 PCS	9.42	9.32	-0.096 (-2.98 to 2.79)	0.95
EuroQoL-5	0.086	0.102	0.016 (-0.046 to 0.077)	0.62
HUI-3	0.068	0.094	0.026 (-0.043 to 0.095)	0.46

MOS SF-36: Medical Outcome Study Short Form 36; MCS: Mental Component Summary; PCS: Physical Component Summary; EuroQol-5: EuroQoL 5 dimension 3 level version; HUI-3: Health Utilities Index Mark 3

meaning that hysterectomy is 100% and UAE is >75% clinical effective in the treatment of menorrhagia [7]. Furthermore, no systematic difference in health-related quality of life nor in health state valuations (utilities) between strategies were found up to 24 months follow-up, a consistent finding for all measures of Health Related Quality of Life (HRQOL) that were studied [MOS SF-36 [8]; EuroQol 5 [9]; HUI-3 [10]] [13] (Table 1). Furthermore, we found no evidence for any differences in the subsequent occurrence of menopausal symptoms between the two strategies [14].

Since no difference was found in clinical effectiveness and quality of life between the treatment strategies, a cost-minimization analysis was considered to be the appropriate economic evaluation framework.

Cost-minimization analysis (CMA)

Costs were defined as the volumes of resources used during two years of follow-up multiplied by the price per unit of each resource. Using the societal perspective we considered four cost categories: (i) direct medical costs in-hospital costs (e.g. pre-procedural costs, in-hospital costs related to the intervention, any additional in-hospital medical costs during follow-up); (ii) direct medical costs out-of-hospital costs (e.g. unscheduled general practitioner visits and use of medication out of hospital); (iii) direct non-medical costs (patient expenses such as travel costs and sanitary measures); and (iv) indirect costs (productivity related costs due to absence from work).

Data on resource use were collected prospectively in a case record form and as part of the patient's self-report questionnaires at 6 weeks, 6, 12, 18 and 24 months after the primary intervention.

The costs per unit of used resources were obtained from various data sources. The unit costs of direct medical in-hospital cost volumes were based on 'true' economic cost calculations as obtained from the hospital management system in the Academic Medical

Centre, Amsterdam [15]. 'True' economic costs include a share of fixed costs as well as shares of departmental and hospital overhead costs. Using these unit costs as standard valuations eliminated cost variability due to differences between hospitals. The cost volumes of UAE and hysterectomy were based on detailed micro-costing using data recorded in the case record forms and patient records in all participating hospitals. The cost volumes related to complications were recorded prospectively in the case record form (e.g. type of complication, unscheduled outpatient visit, subsequent diagnostic and therapeutic measures) and afterwards graded with the use of the classification system of the Society of Interventional Radiology, as recommended in the Standard of Practice [16].

Resource use and costs related to study purposes only, which were not part of routine clinical care (e.g. part of laboratory investigations; additional ultrasonography and MRI performed after the primary procedure) were excluded from the present analysis. Two follow-up visits after UAE (at 1 week and 6 weeks after the primary intervention) and one follow-up visit after hysterectomy (at 6 weeks after the intervention) were considered as standard care and were included in our cost analysis. Any further follow-up visits conducted for study purposes were excluded from our analysis, unless these were unscheduled follow-up visits for medical problems related to the primary intervention.

The unit costs of direct medical out-of-hospital costs, direct non-medical costs and indirect costs were based on Dutch guidelines for cost calculations in health care [17;18]. Indirect costs due to absence from work were estimated as the actual working time lost (hours) multiplied by the reported average net income according to the friction cost method [17]. Travel costs per patient were based on mean distances to hospitals (7.0 km) and to general primary care units (1.8 km) [17]. Costs were originally calculated in Euros, updated to the 2005 price level by using the Dutch Consumer Price Index (www.cbs.nl) and then converted into U.S. dollars (€1.00 = US$1.34). A 4% discount rate was applied to costs that occurred after 12 months [17].

SENSITIVITY ANALYSIS

One-way sensitivity analysis was performed to examine the impact of a chosen variable on the total cost difference between strategies by varying it across a range of plausible values [19]. We varied four parameters which represented the largest and/or most variable costs: 1) duration of in-hospital stay; 2) duration of absence from work; 3) minor complication rate during follow-up; and 4) incidence of secondary hysterectomies after UAE for insufficient symptomatic relief. The low and high values in the sensitivity analysis correspond to the lower and upper limit values of the 95%CI of the respective variables as found in our study population.

Parameters 1 and 2 are subject to differences between various health care systems across different countries, i.e. associated costs may not reflect those in other centers over the

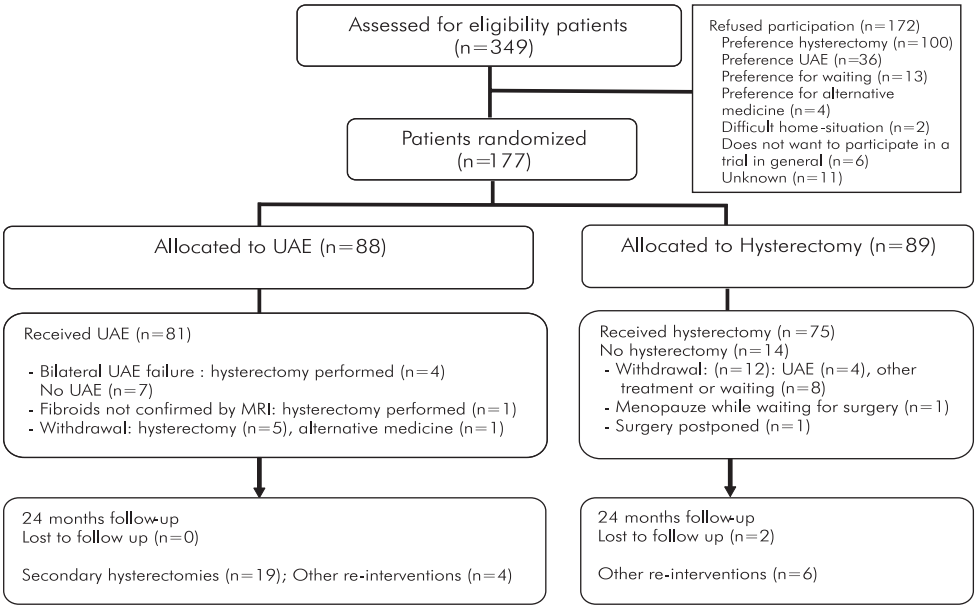
world. Parameters 3 and 4 might change in time due to improved techniques/materials or expertise.

STATISTICAL ANALYSIS

Data were recorded and analyzed using SPSS statistical software (version 11.5.1). Study outcomes were analyzed according to original treatment assignment (intention to treat). Costs were described with descriptive statistical measures: means, mean differences, and 95% confidence intervals (95%CI). The 95%CI of the differences in mean costs between strategies were obtained by non-parametric bootstrap method including the correction for bias and acceleration [20] applied to the following six cost categories: (1) costs from the pre-procedural work up, the primary intervention and the post-procedural care; (2) costs from discharge until 2 years' follow-up; (3) direct medical in-hospital costs (=(1)+(2)); (4) direct medical out-of-hospital costs plus direct non-medical costs; (5) indirect costs; and (6) total costs (=(3)+(4)+(5)). The analyses were based on a 1000 bootstrap samples of the two separate groups.

A p-value < 0.05 (two-tailed) was considered statistically significant.

FIGURE 1. Flowchart



RESULTS

PATIENTS

Patients were included between March 2002 and February 2004 in 28 Dutch hospitals [21]. Of 349 eligible patients, 177 were randomized: 88 were allocated UAE and 89 hysterectomy. After withdrawal, 81 women underwent uterine artery embolization and 75 underwent hysterectomy (Figure 1).

The mean age of participating patients was 44.6 years (UAE group) and 45.4 years (hysterectomy group). Participants were predominantly white: 61.4% and 64.0% for UAE and hysterectomy respectively. Most patients (85.3%) had received at least one treatment before study enrolment. Patients suffered from menorrhagia for a median of 24 months. Although the main inclusion criterion was menorrhaghia complaints, the majority of patients also had pain (UAE: 82.9%; hysterectomy: 68.5%) and bulk-related complaints (UAE: 77.3%; hysterectomy: 75.3%). Logistic regression analysis did not reveal baseline characteristics that could predict randomization outcome, thereby confirming successful randomization (Table 2).

TABLE 2. Baseline and procedural characteristics

	UAE (n=88) n (%)	Hysterectomy (n=89) n (%)
BASELINE CHARACTERISTICS		
Age (years)		
Mean (SD)	44.6 (4.8)	45.4 (4.2)
Body Mass Index (weight (kg) / length (m^2)		
Mean (SD)	26.7 (5.6)	25.4 (4.0)
Parity		
0	30 (34.1)	20 (22.5)
1/>1	58 (65.9)	69 (77.5)
Ethnicity		
White	54 (61.4)	57 (64.0)
Black	24 (27.3)	20 (22.5)
Other	10 (11.4)	12 (13.5)
Smoking status		
Current smoker	21 (23.9)	23 (25.8)
Former smoker	11 (12.5)	14 (15.7)
Non-smoker	56 (63.6)	52 (58.4)
Highest educational level *1		
Elementary school	3 (3.4)	6 (6.9)
Lower vocational, lower secondary school	29 (33.0)	32 (36.8)
Intermediate and higher vocational, higher secondary school	26 (29.5)	27 (31.0)
College/University	28 (31.8)	22 (25.3)
Other	2 (2.3)	0 (0)
Paid work	68 (77.3)	70 (78.7)

TABLE 2. continued

		UAE (n=88) n (%)	Hysterectomy (n=89) n (%)
Previous treatment *2			
None		11 (12.5)	15 (16.9)
Hormonal		59 (67.0)	59 (66.3)
Non-Steroidal-Anti-Inflammatory-Drugs /Tranexaminacid		45 (51.1)	41 (46.1)
Iron-supplement/blood transfusion		50 (56.8)	52 (58.4)
Surgical procedures		17 (19.3)	11 (12.4)
Myomectomy		13 (14.8)	13 (14.6)
Hysteroscopic endometrium resection		3 (3.4)	1(1.1)
Curettage		3 (3.4)	0 (0)
Symptoms			
Menorrhagia		88 (100)	89 (100)
Anemia		43 (48.9)	42 (47.2)
Lower abdominal pain		73 (82.9)	61 (68.5)
Bulk-related complaints		68 (77.3)	67 (75.3)
Duration of symptoms (months)			
Median (range)		24 (3-250)	24 (4-240)
Duration of menstruation (days)			
Total days (median, range)		7 (4-28)	8 (3-42)
Heavy days (median, range)		3 (1-28)	4 (1-21)
Modified pictorial blood loss assessment chart (PBAC)			
Median (IQR)		850 (429-1483)	952 (475-1453)
Number of fibroids *3			
Median (range)		2 (1-20)	2 (1-9)
PROCEDURAL CHARACTERISTICS			
Type of UAE			
Target embolization	Left uterine artery	65	-
	Right uterine artery	59	-
Selective embolization	Left uterine artery	8	-
	Right uterine artery	12	-
Type of hysterectomy		(n=4)	
Abdominal hysterectomy		(2)	63
Vaginal hysterectomy		(1)	8
Vaginal hysterectomy with morcellator		(1)	1
Laparoscopic hysterectomy with morcellator		-	2
Laparoscopic assisted vaginal hysterectomy		-	1
Cervix			
Conservation of cervix		(2)	22

Data were available for all or all but 1 patient, unless stated otherwise; Number of fibroids was calculated by ultrasound; *1 hysterectomy missing: 2; *2 patients may have had more than one previous treatment or more than one fibroid-related symptom ;*3 UAE missing: 5, hysterectomy missing: 11. Logistic regression did not reveal baseline characteristics that could predict randomization outcome.

TABLE 3. Resource use from randomization until 24 months follow-up

Resource use	UAE (n=81)		hysterectomy (n=75)	
	number	unit cost $	number	unit cost $
Direct medical in-hospital costs				
Prior to primary procedure				
Pre-procedural work up *[1]	81	668	75	462
Primary procedure				
successful embolization	77	2356	0	2356
bilateral failed embolization	4	2090	0	2090
hysterectomy	0	3829	75	3829
epidural anesthesia	13	388	21	388
peri-procedural minor complications	5	0	2	0
peri-procedural major complications	0	0	0	0
post-procedural admission nursing ward				
admission nursing ward (mean duration of hospital stay/days)	81 (1.7)	987	75 (5.1)	2952
minor complications during admission	92	904	112	271
major complications during admission	1	6328	1	6328
From discharge until 24 months follow-up				
scheduled outpatient visit	162	168	75	168
unscheduled outpatient visits	107	168	63	168
minor complications during follow-up	168	251	104	243
major complications during follow-up	4	134	1	2072
readmission nursing ward (mean duration of hospital stay/days)	27 (5.4)	3165	6 (4.6)	2680
re-intervention: secondary hysterectomy	19	3829	0	3829
re-intervention: other	4	1675	6	2770
Direct medical out-of-hospital costs				
unscheduled general practitioner visits	18	27	18	27
prescribed medication	36	155	5	5
Direct non-medical costs				
travel costs	81	39	75	26
tampons and sanitary napkins	73	112	0	0
Indirect				
absence from work (mean duration of absence of work/days)	61 (21)	6368	50 (46)	15384

RESOURCE USE

Table 3 details the main volumes of resource use as well as the unit costs per resource. In the UAE group 4 of 81 embolizations (4.9%) were bilateral technical failures, resulting directly in a secondary hysterectomy. In the hysterectomy group the types of hysterectomy that were performed were as follows: abdominal hysterectomy 63/75 (84%); vaginal hysterectomy 9/75 (12%); laparoscopic hysterectomy 2/75 (3%); laparoscopically assisted vaginal hysterectomy 1/75 (1%).

All secondary hysterectomies but one were performed because of persistence or relapse of menorrhagia. In one patient menorrhagia resolved, but pain and bulk-related complaints

worsened, and necessitated a secondary hysterectomy. These hysterectomies were evenly distributed over the two year follow-up period.

The following re-interventions, apart from secondary hysterectomies, were performed: hysteroscopic fibroid resection (n=1); manual fibroid resection (n=1); diagnostic hysteroscopy with curettage (n=1); adhesiolysis via laparotomy (n=1); bilateral adnex extirpation (n=1); fistula repair (Latzko technique) (n=1); (laparoscopic) cicatrix reconstruction surgery (n=2); adhesiolysis combined with ovarian cystectomy via laparotomy (n=1); diagnostic laparoscopy (n=1).

Concerning the direct medical cost volumes, noticeable results were the following: additional epidural anesthesia was more often applied in the hysterectomy group (13/81 vs. 21/75); patients in the hysterectomy group were significantly longer hospitalized (1.7 vs. 5.1 days); readmissions occurred more frequently in the UAE group (27/81 vs. 6/75); in total 19 secondary hysterectomies were performed in the UAE group because of bilateral technical failure (n=4) or clinical failure (n=15); nearly twice as much unscheduled outpatient visits occurred in the UAE group (107/81 vs. 63/75).

Regarding the direct non-medical costs, the mean number of tampons and sanitary napkins used in the UAE group were 163 and 442 per woman, respectively. Absence from work was 21 days for UAE patients and 46 days for hysterectomy patients on average. The costs of a successful embolization and a bilaterally failed embolization differed only slightly ($2356 vs. $2090, respectively), which was mainly based on the use of polyvinyl alcohol particles or not.

RESOURCE COSTS PER PATIENT

Table 4 shows the mean costs per patient for each cost parameter and for each cost category (direct medical in-hospital; direct medical out-of-hospital; direct non-medical; indirect), and in total. The average total costs of the UAE strategy consisted of direct medical in-hospital costs (58%), direct medical out-of-hospital costs (0.6%), non-medical costs (1.2%) and absence from work (41%). In the hysterectomy group, these proportions were 45%, 0.2%, 0.1% and 55% respectively. The mean total costs of UAE were significantly lower than those of hysterectomy (mean cost difference: - $6936 (-37%), 95%CI: [- $9548 to - $4281]. The difference in total costs (- $6936) could be attributed chiefly to the difference in direct medical in-hospital costs (- $1624, 95%CI: [- $2605 to –$586]) and indirect costs (- $5453, 95%CI: [- $7718 to - $3107]) between the procedures which were both significantly lower for the UAE strategy. The costs related to the primary interventions including pre- and post procedural care were also significantly lower for the UAE ($4157) than for hysterectomy ($7538; mean cost difference: - $3381, 95%CI [- $3772 to - $2860]). The cost advantage for UAE was partly offset by the subsequent costs generated during two years of follow-up,

TABLE 4. Average costs per patient at 2 year follow-up

	UAE n=81 mean ($)	Hysterectomy n=75 mean ($)	mean difference ($)	95%CI mean difference ($)
Direct medical in-hospital costs				
Costs pre-procedural work-up	668	462	206	
Costs primary procedure	2417	3945	-1528	
Costs postprocedural care	1071	3130	-2059	
Subtotal pre-preprocedural, primary procedure and post procedural costs	4156	7537	-3381	-3772 to -2860
Costs from discharge until 2 years follow-up	2532	775	1757	781 to 2629
Total direct medical in-hospital costs	**6688**	**8313**	**-1625**	-2605 to -586
Direct medical out-of-hospital costs	74	33	41	
Direct non-medical costs	140	26	114	
Total direct medical out-of hospital and non-medical costs	**214**	**59**	**155**	99 to 237
Indirect costs	4723	10176	-5453	
Total indirect costs	**4723**	**10176**	**-5453**	-7718 to -3107
Overall total costs	**11626**	**18563**	**-6937**	-9548 to -4281

(1 euro = 1,34 US$;)* 95%CI were obtained with the non-parametric bootstrap method. The 95%CI presented include adjustment for bias and acceleration

which were significantly higher after UAE than after hysterectomy (mean cost difference: $1757, 95%CI: [$781 to $2629]).

Significant cost differences between both groups for the separate cost parameters were as follows: Costs of pre-procedural outpatient visits were higher for UAE (mean difference $206). With regard to costs of post-procedural unscheduled outpatient visits, readmissions and secondary hysterectomies as re-intervention, UAE was more costly than hysterectomy (mean difference $170, $721 and $898, respectively). Costs of the primary procedure (i.e. UAE and hysterectomy) were lower for UAE than for hysterectomy (mean difference - $1528).

SENSITIVITY ANALYSIS

Table 5 displays the impact of alternative assumptions about four cost parameters on the mean total cost difference between both treatment modalities. The total cost difference was relatively insensitive to variations in the length of hospital stay and to the variation of minor complication rates. Two parameters were somewhat sensitive to variation across values different from base-case values: the duration of absence from work and the rate of secondary hysterectomies. For all assumed variations, however, a difference in total costs remained in favor of UAE.

TABLE 5. Sensitivity analysis*[1]

Variable		UAE		Hysterectomy			
		value	total mean costs ($)	value	total mean costs ($)	mean difference in total costs ($)	% change
duration of hospital stay (days)	observed	1.7	11626	5.1	18563	-6937	
	low	1.3	11394	4.8	18389	-6995	0.80%
	high	2	11800	5.4	18737	-6937	0%
absence from work (days)	observed	21	11626	46	18563	-6937	
	low	16	10110	36	15219	-5109	-35.80%
	high	27	13445	56	21907	-8462	22.00%
minor complications during follow-up	observed	2.10%	11626	1.40%	18563	-6937	
	low	1.80%	11590	1.10%	18511	-6921	-2.30%
	high	2.40%	11662	1.70%	18615	-6953	2.30%
secondary hysterectomy rate	observed	23.50%	11626	--	18563	-6937	
	low	14.80%	11037	--	18563	-7526	8.50%
	high	34.20%	12358	--	18563	-6205	-11.80%

Cost figures are in US$. *[1] low and high values of the variables varied correspond to the lower and upper limits of the 95%CI of the respective variables *[2] including duration of hospital stay

A threshold analysis showed that direct medical and non-medical costs of the strategies were equal at a 55.2% overall clinical success rate of UAE. At success rates beneath this level, hysterectomy became the cheapest treatment.

DISCUSSION

Our study shows that, as a treatment for heavy menstrual bleeding, UAE is a cost-saving alternative to hysterectomy in women with uterine fibroids. Health outcomes did not differ between strategies but mean total costs per patient were 37% lower for UAE compared to hysterectomy. Differences in direct medical in-hospital costs contributed to this difference to a considerable extent; the costs of the embolization procedure were lower than costs of a hysterectomy. Surprisingly, indirect costs were an even more important contributor to the difference in total costs. Absence from work accounted for 79% of the overall difference in total costs. According to the sensitivity analysis, overall cost differences were relatively insensitive to variations in four important cost parameters, implying that the cost difference in favor of UAE was robust.

The few available published reports concerning the costs and cost-effectiveness of UAE have been limited to retrospective, single centre studies, which only reported direct medical in-hospital costs [22-24]. Only one of those studies concluded that the in-hospital costs of UAE

were higher for UAE than for hysterectomy in the treatment of uterine fibroids [25]. The increased costs of UAE in that study were mainly related to complications; one patient was readmitted for severe pain while another patient went into respiratory arrest after UAE. Furthermore post-procedural pelvic MR imaging for study purposes was included in the total costs as well. In agreement with our results, the majority of other reports suggested UAE to be associated with lower costs than hysterectomy [22-24;].

One report has also performed an economic evaluation from the societal perspective, including both direct and indirect costs [23]. That study was based on a decision model using assumptions and estimates as input, rather than being based on real observations from a prospective randomized trial. Despite these methodological differences between that study and ours, the results were very similar, and also confirmed UAE to be a cost-effective alternative to hysterectomy.

Only recently, another empirical cost-effectiveness analysis comparing UAE and hysterectomy or myomectomy in a randomized trial design, was published, the Scottish REST trial [26]. In this study, after one year of follow-up, UAE was found to be less costly than surgery (mean difference: $1712). This is comparable to our findings, where these costs differed by $1625 in favor of UAE. However, as illustrated by our findings, the true difference in costs between UAE and hysterectomy is much larger when a longer follow-up is considered, and when absence from work is entered in the equation.

When comparing the results of economic evaluations between countries, researchers are confronted with the issue of external validity (generalizability). Various factors cause differences in costs of medical treatments between countries, which are related to either healthcare resource use or cost per units of provisions and performances [17]. On the whole, published reports on costs of UAE and/or hysterectomy suggest direct medical in-hospital costs for both UAE and hysterectomy to be strikingly lower than the direct medical in-hospital costs as calculated in our study [22;23;27-29]. Studies comparing hysterectomy with other treatment alternatives including both direct medical in-hospital and out-of-hospital costs also seem to suggest lower costs for hysterectomy [30;31]. Similarly, lower costs of hysterectomy were reported in two studies which considered both direct and indirect costs [32;33].

There are several explanations for the apparently lower costs of both UAE and hysterectomy as reported by others in comparison to our findings. Firstly, most previous reports used cost estimations in their economic evaluation. Part of the fixed costs and shares of departmental and hospital overheads that should be allocated in part to the cost volumes are vulnerable to being easily overlooked when costs are estimated instead of being calculated. Cost estimations may therefore systematically underestimate 'true' economic costs, as used in our

analysis [15]. Secondly, several resource volumes were not included in earlier studies due to retrospective data collection, which is prone to underestimation of used resources.

Absence from work accounted for 79% of the difference in total costs between UAE and hysterectomy. This implies that performing an economic evaluation from a societal perspective may lead to unexpected, yet very important findings. Only one other study comparing UAE and hysterectomy included indirect costs or productivity costs in its economic evaluations [23]. This is surprising because indirect costs contribute substantially to the costs for society when a particular treatment choice is being made.

One potential limitation is that our findings may be typical for the Dutch healthcare system and insurance legislation regarding absence from work, which differs from the United States and from other countries within Europe. When assuming 16 days absence for UAE and 36 days for hysterectomy in the sensitivity analysis, the differences in total costs decreased by 17%. Even with these assumptions, the total cost difference changed, but the mean total costs of UAE were still lower than those of hysterectomy.

An important limitation of our economic evaluation is that UAE was performed according to the state of the art at the onset of the study. Since then, the technique of UAE has been further developed and in some institutions pre-procedural MRI/MRA is now being used to detect vascular anomalies as part of patient selection. Also, direct post-procedural MRI scans are sometimes being performed to detect the fibroid infarction rate, thus indicating the need for any re-embolizations in case of unsatisfactory technical or clinical [34]. These developments may increase the clinical success rate of UAE even further, at the expense however, of extra costs.

Another limitation of our evaluation is that data were not collected beyond 2 years of follow-up. Relief of symptoms related to fibroids usually occurs after menopause [1]. Hence, follow-up of patients until menopause would seem more appropriate. Reassuringly, any differences in clinical outcome, health status and health-related quality of life, were absent between 6 and 24 months of follow up. It remains unclear, however, whether our results will remain stable beyond this observation window, until menopause. Longer follow-up the EMMY trial cohort is warranted to determine long-term cost differences. Long term follow-up of two other case series showed the 5-year success rate of UAE to range between 73% and 75% [35;36]. Until today no economic evaluation comparing UAE and hysterectomy has been published with a follow-up exceeding 12 months, except for one decision-analytic approach, that estimated costs and effects until menopause [23].

In summary we can state that the 24 months mean costs of UAE were lower for UAE compared to hysterectomy, mainly due to the differences in direct medical in-hospital costs and indirect costs. According to the sensitivity analysis, overall cost differences were relatively insensitive to variations in four important cost parameters, implying that the cost difference in favor of

UAE was robust. Therefore, we conclude that from an economic perspective, uterine artery embolization is the superior treatment strategy for patients with symptomatic uterine fibroids.

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UTERINE ARTERY EMBOLIZATION VERSUS HYSTERECTOMY IN THE TREATMENT OF SYMPTOMATIC UTERINE FIBROIDS (EMMY TRIAL): TREATMENT BURDEN AND PATIENTS' PREFERENCES

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ABSTRACT

Objective

To prospectively evaluate patient preferences and treatment burden of hysterectomy relative to uterine artery embolization (UAE) before and after treatment and to study the effect of preference on quality of life and satisfaction.

Methods

Twenty-eight Dutch hospitals recruited 177 patients with symptomatic uterine fibroids and menorrhagia, who were eligible for hysterectomy. Patients were randomly allocated UAE (n=88) or hysterectomy (n=89). Patients' preferences and treatment burden were assessed both prior and after treatment until 24 months thereafter. Differences in categorical data were tested with χ^2-tests/ Fisher Exact tests. Differences in paired categorical data were tested with Wilcoxon matched pairs test. The impact of covariates on preferences and preference shift was analyzed with binary logistic regression. Multiple linear regression was used to analyze the effect of preference on health related quality of life with the use of the MOS SF-36.

Results

Before randomization, the anticipated burden of hospital admission, pain and discomfort were perceived more burdensome for hysterectomy than for UAE (respectively p=0.03, p=0.03, p=0.0003). Experienced burden after treatment was lower for all parameters than anticipated at baseline and did not differ significantly for most parameters between the groups.

At baseline 63/88 (75.0%) of UAE and 52/89 (63.4%) hysterectomy patients preferred UAE (p=0.12). After 24 months 56/80 (70.0%) of patients in the UAE group and 15/73 (20.5%) patients in the hysterectomy group preferred UAE (p<0.0001). 40% of patients shifted preference compared to baseline. There was no effect of having received the preferred treatment or not on quality of life (difference in SF-36 PCS and SF-36 MCS change scores; p=0.51 and p=0.71) nor on satisfaction ratings (p=0.34) at 24 months.

Conclusion

At baseline, most study participants preferred UAE before randomization. At 24 months follow-up patients predominately preferred the treatment they had been allocated to. Since the primary and secondary clinical outcomes and quality of life did not differ, patients' treatment preferences should play a decisive role in the selection of treatment.

INTRODUCTION

Uterine artery embolization (UAE) for the treatment of heavy menstrual bleeding caused by uterine fibroids was first described in 1995 [1]. Recently, we reported the 2 years outcome of a large prospective, multi-center, randomized trial comparing UAE with hysterectomy for patients with symptomatic fibroids. UAE was shown to be a valuable alternative treatment, preventing hysterctomy in 76.5% of patients [2]. Major complication rates were low in both treatment groups. The in-hospital stay was significantly shorter in embolized patients, at the expense, however, of a higher re-admission rate [3]. Although we found no difference in health-related quality of life after 2 years follow-up, hysterectomy patients were significantly more satisfied [4]. Another recently published randomized trial comparing UAE and surgery after a 1-year follow-up period reported similar findings [5].

Although the clinical and health outcomes hardly differ between both treatments, some other characteristics of the two differ considerably. Hysterectomy is an operative procedure with a longer hospital stay and recovery time but guarantees, with full certainty, cure of menorrhagia complaints at the expense of the loss of the patient's uterus [6]. UAE, in contrast, is regarded as being a less invasive procedure preserving the patient's uterus, with shorter hospital stay and recovery time, at the expense however, of a lower clinical success rate which may necessitate a hysterectomy for some women at a later stage.

In view of these differences, patients' preferences may play a decisive role in treatment choice [7]. Patient's perceptions of treatment burden and benefits of therapy may vary between patients and may also differ between patients and health professionals [8].

The objective of the present study was to prospectively evaluate patients' treatment burden and preferences of UAE relative to hysterectomy, prior to and after having received the allocated treatment. We also investigated which parameters had an effect on baseline preferences, 24 months preferences and analyzed which parameters were associated with a shift in treatment preference. Finally, we investigated whether receiving the treatment of choice had any influence on health-related quality of life or satisfaction at 24 months follow-up.

METHODS

PATIENTS

The EMMY (EMbolization versus hysterectoMY) study is a multi-centre randomized trial, conducted in the Netherlands, where 28 hospitals participated in the trial. Patients were included if: 1) the clinical diagnosis of uterine fibroids had been confirmed by ultrasonography,

2) menorrhagia was the predominant complaint among pain and bulk-related complaints, 3) hysterectomy was thought to be the ultimate solution and other treatment options were unsuitable or had failed to provide symptomatic relief, 4) they were premenopausal, 5) preservation of the uterus was not warranted for future pregnancy, 6) the following disorders were absent: renal failure (creatinine >150 mmol/L), active pelvic infection, clotting disorders, allergy to contrast fluid, (suspected) uterine malignancy, submucosal fibroids protruding by >50% within the uterine cavity or pedunculated abdominal fibroids.
According to Dutch guidelines the study was approved by the Central Committee Involving Human Subjects (www.ccmo.nl) and by local ethics committees of participating hospitals.

TREATMENT INFORMATION

All patients eligible for trial participation were informed prior to randomization about the risks and benefits of both procedures based on data from the literature available at study onset (2002). They also received standardized oral and written information. Hysterectomy was described as a procedure performed under general anesthesia with 1) 5-7 days in-hospital stay; 2) recovery time around 6 weeks; 3) 100% success rate for heavy menstrual bleeding problems; 4) and a (unspecified) risk of complications such as infection, premature ovarian failure or urinary incontinence. UAE was described as a minimal invasive technique, performed under local or epidural anesthesia with 1) 1-2 days in-hospital stay; 2) recovery usually within 2 weeks; 3) an about 80% likelihood of resolving menorrhagia complaints; 4) an uterine volume reduction of about 50%; 5) and an (unspecified) risk of infection, premature ovarian failure or need for additional surgical intervention.

After written informed consent was obtained, patients were randomly assigned (1:1) to UAE or hysterectomy. Next, all patients underwent a clinical evaluation, including a physical examination, a pelvic ultrasound and blood work before treatment. In addition, UAE patients underwent a pelvic MRI scan prior to the procedure.

UAE PROCEDURE

UAE was performed under local or epidural/spinal anesthesia. Women were admitted to the gynecology ward for peri-procedural care. For pain control, patients received paracetamol and NSAIDs before, during and after UAE, with additional opiates or epidural anesthesia if necessary. After the procedure, patients stayed in hospital for at least one night. At discharge, patients no longer required opiates for sufficient pain relief. At discharge, patients were instructed on pain medication regimens while instructions in writing were provided on when and how to contact the gynecologist in case of uncontrollable pain, persistent fever or other problems.

HYSTERECTOMY

The type of hysterectomy and the route of access were left at the discretion of the attending gynecologist. The following procedures were allowed: abdominal hysterectomy, either by median or a pfannenstiel incision, vaginal hysterectomy, laparoscopically assisted vaginal hysterectomy and laparoscopic hysterectomy. The type of anesthesia and further pain management was according to local protocols. Patients were admitted to the gynecology ward for peri-operative care. At discharge, patients no longer required opiates and hysterectomy patients received similar instructions as the UAE patients.

Regardless of allocated treatment, all patients were routinely seen at the gynecology outpatient clinic at 6 weeks and 6, 12, 18 and 24 months after treatment.

PREFERENCES AND TREATMENT BURDEN

Patient's preferences and treatment burden were assessed by means of a patient survey at baseline (i.e. after consent was obtained, before randomization). Follow-up questionnaires were administered at 6 weeks and 6, 12, 18 and 24 months after primary treatment.

The baseline questionnaire comprised the following: 1) the anticipated likelihood of clinical success of both procedures in the treatment of menorrhagia complaints, both quantitatively (99%, 98%, 96%, 93%, 90%, 85%, 80%, 75%, 70%, 60% and 50%) and subjectively (using a three-point Likert scale: 'high', 'reasonably high' and 'not high'; 2) patient's treatment preference: preference for hysterectomy, for UAE or indifferent between hysterectomy and UAE; 3) anticipated burden of each procedure in terms of: a) in-hospital stay, b) pre-procedural work-up, c) anesthesia, d) the procedure itself, e) pain after the procedure, f) complication(s) after the procedure, g) discomfort after the procedure, and h) the possible persistence/recurrence of menorrhagia complaints after the procedure (only in the UAE group). Patients were invited to rate the anticipated burden on a three-point Likert scale: 'none to slight', 'moderate', 'severe to very severe'; and finally 4) Medical Outcome Short Form 36 (MOS SF-36) health survey comprising physical health and mental health (PCS and MCS respectively) [9].

The follow-up survey addressed the following aspects: 1) experienced burden of the received treatment, which was recorded at 6 weeks and 6 months after treatment; 2) patient's treatment preference. Since treatment preference might depend on the UAE clinical success rate, we presented treatment options as a series of two juxtaposed descriptions ('vignettes'), one for hysterectomy and one for UAE. For each pair of vignettes, hysterectomy was the standard treatment with an expected 100% clinical success for menorrhagia while the clinical success rate of UAE varied from 60% to 98%. For each pair of vignettes, treatment preference was recorded on a three-point Likert scale: preference for hysterectomy, for UAE or indifferent;

3) MOS SF-36 health survey; 4) overall treatment satisfaction recorded on a seven-point Likert scale: 'very satisfied', 'satisfied', 'moderately satisfied', 'not satisfied nor unsatisfied', 'moderately unsatisfied', 'unsatisfied' or 'very unsatisfied'.

STATISTICAL ANALYSIS

Data entry was performed using SPSS data entry for Windows 3.0. A random sample of 10% of the questionnaires was visually double checked by an independent second investigator revealing a false entry level of 0.3%. All false data entries were corrected. Analyses were done using SPSS statistical software (version 11.5.1).

Study outcomes were analyzed according to original treatment assignment (intention to treat). Differences in prior and post-procedural preferences and anticipated and experienced burden were expressed in n (%). Differences in categorical data between the groups were compared with χ^2-tests or Fisher Exact tests if appropriate. Differences in paired categorical data within patients were tested with Wilcoxon matched pairs test. Differences in proportions between the treatment groups were tested with univariate binary logistic regression.

Multiple binary logistic regression was used to investigate the effect of various covariables on baseline preferences: hysterectomy vs. UAE, disregarding indifference [model I]. Co-variables entered in the multivariable model were variables yielding p-values <0.10 in the univariate analysis. The following variables were included in the univariate analysis: age (continuously), BMI (continuously), ethnicity (caucasian/non-caucasian), parity (parous/non-parous), current smoking (yes/no), educational level (intermediate/higher level vs. lower level), married (yes/no), paid work (yes/no), comorbidity (yes/no), uterine volume (continuously), number of fibroids (continuously), previous surgical treatment (yes/no), any previous treatment (yes/no), duration of menorrhagia symptoms (continuously), hemoglobin level (continuously), anemia before treatment (yes/no), baseline SF-36 MCS and SF-36 PCS (continuously), anticipated burden of various aspects of hysterectomy (low/medium/high), anticipated burden of various aspects of UAE (low/medium/high).

Multiple binary logistic regression was also used to evaluate which co-variables were predictive of 24 months treatment preferences (hysterectomy vs. UAE, disregarding indifference) and 24 months satisfaction ('very satisfied'/'satisfied' vs. 'not satisfied' [ranging from 'moderately satisfied' to 'very unsatisfied']) [model II]. These analyses were performed for all patients and for each treatment allocation group separately. The following co-variables were used in the univariate analysis: baseline preference (hysterectomy/UAE), satisfaction at 24 months follow-up ('satisfied'/'not satisfied'), SF-36 PCS and SF-36 MCS change scores compared to baseline (continuously), clinical failure UAE (yes/no; only UAE group), and treatment allocation (hysterectomy/UAE).

Finally, multiple linear regression analysis and multiple binary logistic regression analysis, respectively, were used to investigate if the (dis)agreement between allocated treatment and baseline treatment preference was of any influence on (1) the 24 months SF-36 MCS and PCS change score, and (2) 24 months satisfaction ('very satisfied'/'satisfied' vs. 'not satisfied') [model III]. Treatment allocation matched baseline preference if patients were allocated their preferred treatment as indicated at baseline. Excluded from this analysis were those patients who were indifferent at baseline, those patients with unknown baseline preference, and those patients who withdrew from the trial after randomization. The following variables were entered in the univariate analysis: treatment match (undergoing preferred treatment /undergoing non-preferred treatment) and baseline preferences (having any preference/having no preference). Other co-variables which were predictive of quality of life were already evaluated in an earlier publication [4]. In that report the multiple linear regression analysis revealed no baseline variable to be associated with improvement of MOS SF-36 MCS scores at 24 months. In contrast, being employed significantly enhanced MOS SF-36 PCS at 24 months (Beta: 3.61; 95%CI: 0.26 to 6.96; p=0.035). Logistic binary regression analysis showed improvement in MOS SF-36 MCS scores to be significantly associated with overall satisfaction (p=0.001), while improvement in MOS SF-36 PCS was not (p=0.191).

A two-sided p-value of <0.05 was considered statistically significant in all analyses.

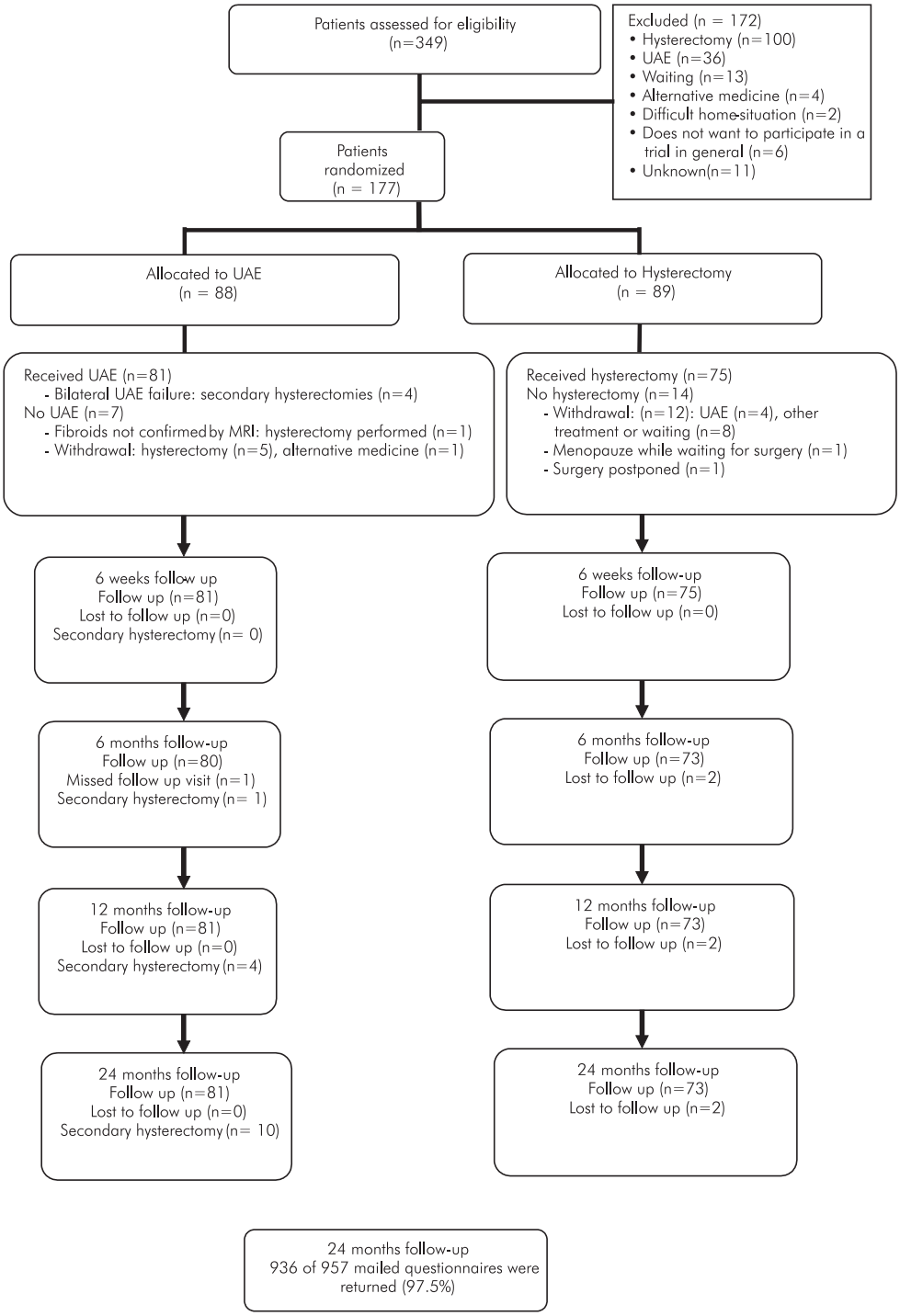
RESULTS

PATIENTS

Patients were enrolled between March 2002 and February 2004. Twenty-eight of the thirty-four participating hospitals included patients. Figure 1 shows the flow of patients through the trial. Of 349 eligible patients, 177 were randomized: 88 were allocated UAE and 89 hysterectomy. The majority of patients refusing trial participation did so for a strong preference for either hysterectomy (58.1%) or UAE (20.9%), while 20.9% refused for other reasons. Seven patients in the UAE group and 14 patients in the hysterectomy group refused the allocated treatment and withdrew participation. Patients who refused the assigned treatment were comparable to participating patients in terms of age, race, BMI, parity, symptoms and duration of symptoms (data not shown). During 24 months follow up, 936 out of 957 (97.8%) mailed questionnaires were returned.

The mean age of participating patients was 44.6 years (UAE group) and 45.4 years (hysterectomy group) (Table 1). Participants were predominantly white: 61.4% and 64.0% for UAE and hysterectomy respectively. Most patients (85.3%) had received at least one

FIGURE 1. Trial profile



treatment before study enrolment. Patients suffered from menorrhagia for a median of 24 months. Other symptoms besides menorrhagia were prevalent. The majority of women had multiple fibroids. Logistic regression analysis did not reveal any baseline characteristics to be predictive of treatment allocation.

TABLE 1. Baseline and procedural characteristics.

	UAE n=88 n (%)	Hysterectomy n=89 n (%)
BASELINE CHARACTERISTICS		
Age (years)		
Mean (SD)	44.6 (4.8)	45.4 (4.2)
Body Mass Index (weight (kg) / length (m^2)		
Mean (SD)	26.7 (5.6)	25.4 (4.0)
Parity		
0	30 (34.1)	20 (22.5)
1/>1	58 (65.9)	69 (77.5)
Ethnicity		
White	54 (61.4)	57 (64.0)
Black	24 (27.3)	20 (22.5)
Other	10 (11.4)	12 (13.5)
Highest educational level *[1]		
Elementary school	3 (3.4)	6 (6.9)
Lower vocational, lower secondary school	29 (33.0)	32 (36.8)
Intermediate and higher vocational, higher Secondary school	26 (29.5)	27 (31.0)
College/University	28 (31.8)	22 (25.3)
Other	2 (2.3)	0 (0)
Previous treatment		
None	11 (12.5)	15 (16.9)
Hormonal	59 (67.0)	59 (66.3)
Non-Steroidal-Anti-Inflammatory-Drugs /Tranexaminacid	45 (51.1)	41 (46.1)
Iron-supplement/blood transfusion	50 (56.8)	52 (58.4)
Surgical procedures*[2]	17 (19.3)	11 (12.4)
Myomectomy	13 (14.8)	13 (14.6)
Hysteroscopic endometrium resection	3 (3.4)	1(1.1)
Curettage	3 (3.4)	0 (0)
Symptoms		
Menorrhagia	88 (100)	89 (100)
Anemia	43 (48.9)	42 (47.2)
Lower abdominal pain	73 (90.1)	61 (81.3)
Bulk-related complaints	68 (84.0)	67 (98.3)
Duration of symptoms (months)		
Median (range)	24 (3-250)	24 (4-240)

TABLE 1. continued

		UAE n=88 n (%)	Hysterectomy n=89 n (%)
Duration of menstruation (days)			
Total days (median, range)		7 (4-28)	8 (3-42)
Heavy days (median, range)		3 (1-28)	4 (1-21)
Modified PBAC score *3			
Median (IQR)		850 (429-1483)	952 (475-1453)
Number of fibroids			
Median (range)		2 (1-20)	2 (1-9)
PROCEDURAL CHARACTERISTICS			
Type of UAE			
Target embolization	Left uterine artery	65	-
	Right uterine artery	59	-
Selective embolization	Left uterine artery	8	-
	Right uterine artery	12	-
Type of hysterectomy		(n=4)	
Abdominal hysterectomy		(2)	63
Vaginal hysterectomy		(1)	8
Vaginal hysterectomy with morcellator		(1)	1
LH with morcellator		-	2
LAVH		-	1
Cervix			
Conservation of cervix		(2)	22

Data were available for all or all but 1 patient, unless stated otherwise. Number of fibroids was calculated by ultrasound unless stated otherwise. *1 hysterectomy missing: 2; *2 The surgical treatments do not add up because some patients had several treatments; *3 UAE missing: 5, hysterectomy missing: 11; Logistic regression analysis did not reveal baseline characteristics that could predict randomization outcome. PBAC: pictorial blood assessment chart

BASELINE PREFERENCES AND ANTICIPATED CLINICAL SUCCESS

Among hysterectomy patients, 52/89 (63.4%) preferred UAE, 10/89 (12.2%) were indifferent, while 20/89 (24.4%) preferred hysterectomy. Baseline preference was unknown in 7/89 (7.9%) patients. In the UAE group, these proportions were 63/88 (75.0%), 8/88 (9.5%), 13/88 (15.4%) and 4/88 (4.5%), respectively. Significant differences between these groups were absent ($p=0.26$ for hysterectomy vs. UAE vs. indifference; $p=0.12$ for hysterectomy vs. UAE).

Compared to patients who declined trial participation, there were significantly more patients who preferred UAE among the trial participants (115/148 [77.7%] vs. 36/136 [26.5%]; $p<0.001$)

Figure 2A and 2B show the anticipated clinical success of both treatments expressed subjectively (high/reasonably high/moderately to low) and quantitatively (success rates ranging from 50% to 99%). Most patients judged the likelihood of UAE being able to solve their complaints as 'high' (48.2%) or 'reasonably high' (40.4%), indicating clinical success rates of > 75% (median: 90; range: 50-99). Eighteen patients (11.4%) judged the clinical

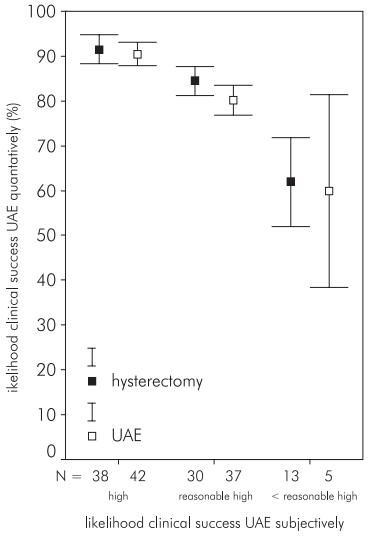


FIGURE 2A. Likelyhood clinical success UAE quantatively and subjectively at baseline

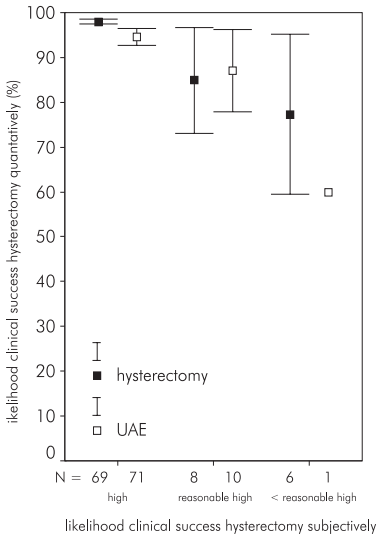


FIGURE 2B. Likelyhood of clinical success hysterectomy quantatively and subjectively at baseline

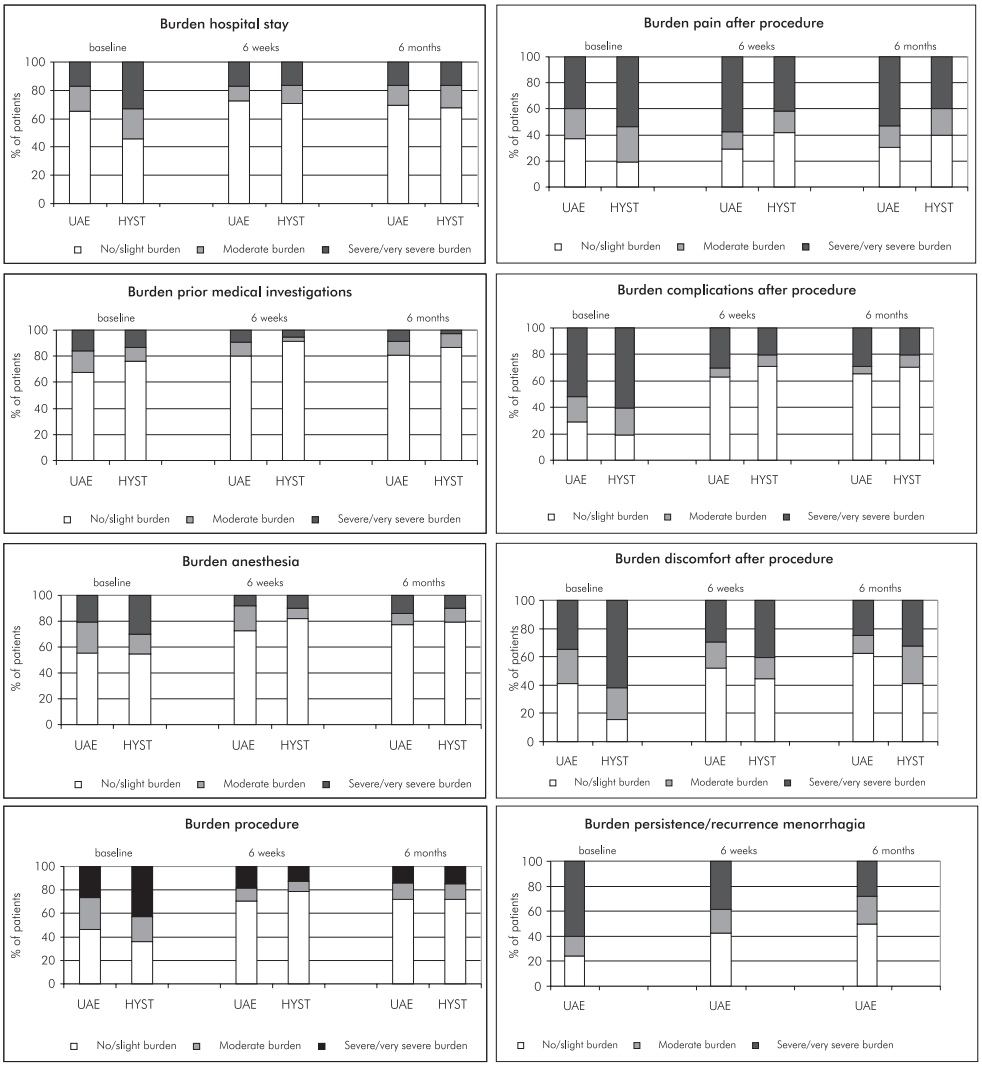
success of UAE as 'moderately to low' with success rates averaging about 60% (median: 50; range: 50-90). For hysterectomy, women considered the likelihood of hysterectomy being able to solve their complaints as 'high' (85.0%) or 'reasonably high' (10.8%). Only 4.2% judged clinical success as 'moderately to low'. The subjectively and quantitively reported clinical success rate of hysterectomy was perceived as being larger than the success rate of UAE (for UAE p=0.0001 and p=0.0002 respectively; for hysterectomy p=0.0003 and p=0.0005 respectively).

The expected clinical success rate of UAE and hysterectomy did not differ between the randomized groups (subjective success of hysterectomy: p=0.47, and UAE: p=0.27; quantitive success rate of hysterectomy: p=0.12 and UAE: p=0.52).

TREATMENT BURDEN

Figure 3 depicts the anticipated and experienced burden of both procedures for the UAE and hysterectomy group separately. At baseline hospital admission, pain and discomfort

FIGURE 3. Anticipated burden at baseline and experienced burden of UAE and hysterectomy at 6 weeks and 6 months for various items



were perceived more burdensome for hysterectomy than for UAE (respectively p=0.03, p=0.03, p=0.0003). Before randomization, patients did not regard the burden related to pre-procedural work-up, anesthesia, the procedures itself or possible complications as being significantly different between the two procedures.

Experienced burden for both treatment options recorded at 6 weeks and 6 months after the procedures was lower than anticipated at baseline for all parameters of burden. UAE was experienced as being less burdensome than anticipated at baseline for the following items at 6 weeks and 6 months respectively: pre-procedural work-up (p=0.04; p=0.06), anesthesia (p=0.01; p=0.03), UAE procedure itself (p=0.008; p=0.002), post-procedural pain (p=0.03; p=0.07), complication(s) (p=0.001; p=0.0001) and possible persistence/recurrence of menorrhagia (p=0.004; p=0.0003). The burden related to post-procedural discomfort and to hospital stay did not differ significantly from what was anticipated at baseline.

Hysterectomy was experienced to be less burdensome for all items at 6 weeks and 6 months compared to baseline: hospital stay (p=0.002; p=0.003), pre-procedural work-up (p=0.03; p=0.02), anesthesia received (p=0.001; p=0.0002), procedure itself (p=0.0002; p=0.0009), post-procedural pain (p=0.007; p=0.01), complication(s) (p=0.0002; p=0.0001) and post-procedural discomfort (p=0.001; p=0.001).

Although most items were scored less burdensome after treatment than expected before treatment, the proportion of patients who scored "severe/very severe" at 6 months was substantial in both groups for post-procedural pain (UAE: 52.8%; hysterectomy 39.7%); discomfort after the procedure (UAE: 25.0%; hysterectomy 32.4%) and post-procedural complications (UAE: 29.1%; hysterectomy 20.6%).

Experienced burden at 6 weeks did not differ significantly between the groups. At 6 months discomfort after hysterectomy was rated significantly more burdensome than after UAE (p=0.01).

PATIENTS' PREFERENCES AFTER TREATMENT

Figure 4A and 4B show patients' preferences for UAE and hysterectomy, expressed by patients from both groups, at 6 months and 24 months follow-up, for varying clinical success rates of UAE.

In both groups at both points in time, the proportion of women preferring hysterectomy increased with decreasing clinical success rates of UAE. At 6 months follow-up, preference for hysterectomy in the UAE group ranged from 7.6% (at 98% clinical success rate of UAE) to 27.8% (at 60% clinical success rate of UAE). At 24 months, 17.5% (at 98% clinical success rate of UAE) to 27.5% (at a UAE success rate of 60%) of patients in the UAE group preferred hysterectomy. In the hysterectomy group, on the other hand, the proportion of

FIGURE 4A. Treatment preference of UAE group at 6 and 24 months follow-up

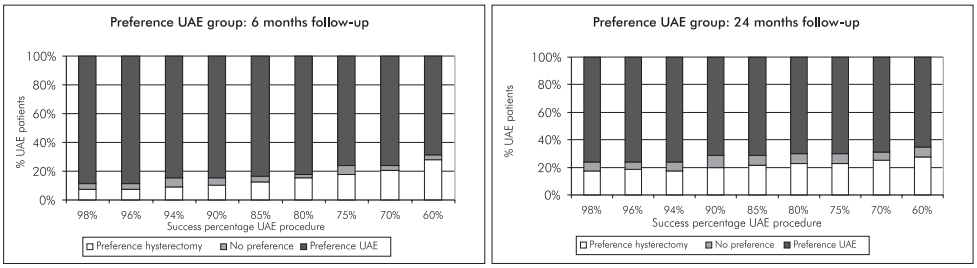
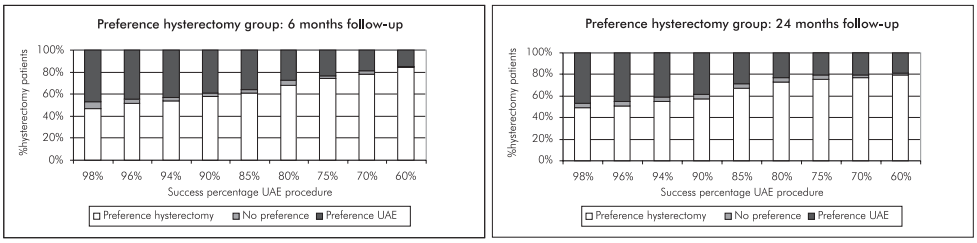


FIGURE 4B. Treatment preference of hysterectomy group at 6 and 24 months follow-up



patients preferring hysterectomy at 6 months ranged from 47.1% (at 98% clinical success rate of UAE) to 84.1% (at 60% clinical success rate of UAE). At 24 months, these proportions were 49.3% and 79.5%, respectively. This inverse relationship was also seen at 6 weeks, 12 and 18 months follow-up (data not shown).

As Figure 4A and 4B illustrate, the proportion of patients preferring hysterectomy at 6 months was larger in the hysterectomy group than in the UAE group (hysterectomy group vs. UAE group [60% UAE clinical success rate: OR=13.66, p=0.0002; 98% UAE clinical success rate: OR=10.85, p=0.0001). Similar results were found at 24 months follow-up.

The actual clinical success rate of UAE as found in our randomized trial was 75% at 24-months follow-up [2]. This implies that 56/80 (70.0%) of patients in the UAE group and 15/73 (20.5%) patients in the hysterectomy group would prefer UAE. 6/80 patients (7.5%) and 3/73 (4.1%) would be indifferent, while 18/80 (22.5%) and 55/73 (75.3%) would prefer hysterectomy, respectively ($p<0.0001$).

PREFERENCE SHIFT

The majority of patients, in both groups and at both follow-up moments, did not shift their preference when the UAE clinical success rate varied. The preferences of patients in the hysterectomy group were more sensitive in response to the varying UAE clinical success rates than those in the UAE group (see Figure 4A and 4B). At 6 months, 27.7% of all patients [UAE: 21.3%; hysterectomy: 34.8%; excluding the patients being indifferent] shifted preference

when the 98% clinical success rate of UAE reduced to 60% (OR=1.97, p=0.08). This means that the odds to shift treatment preference was 1.97 times higher in the hysterectomy group. At 24 months, 22.4% of patients [UAE: 11.0%; hysterectomy: 34.3%; excluding the patients being indifferent] preferred the opposite treatment at a lower clinical success rate of UAE (OR=4.24, p= 0.001). At 24 months the odds to shift treatment preference was 4.24 times higher in the hysterectomy group.

Of the 100 patients who preferred UAE at baseline, 60 (60.0%) still preferred UAE at 24 months while 35 (35.0%) shifted their preference towards hysterectomy. Of the 32 patients who preferred hysterectomy at baseline, 26 (81.3%) also preferred that treatment at 24 months while 6 (18.8%) preferred UAE. Of the 16 patients who were indifferent at baseline, 5/16 (31.3%) preferred UAE, 8/16 (50.0%) preferred hysterectomy and 3/16 (18.8%) were still indifferent (all patients: p=0.0001; hysterectomy: p=0.0001; UAE: p=0.46; Wilcoxon matched pairs).

As Figure 4A and 4B show, the proportion of patients preferring hysterectomy did not change significantly between 6 and 24 months within groups (UAE: p=0.18; hysterectomy: p=0.56; Wilcoxon matched pairs), which indicates that preferences were stable over time.

UAE patients who received a secondary hysterectomy because of unsatisfactory result were more likely to prefer hysterectomy at 24 months compared to patients with a clinically successful UAE (10/15 [66.7%] vs. 8/59 [13.6%]; OR=12.8; p=0.0001).

PREDICTORS FOR PREFERENCES

Three co-variables were predictive of patients' treatment preferences at baseline (model I); Patients with better physical health (high vs. low SF-36 PCS scores) were more enthusiastic about UAE (OR= 1.08; p=0.006). Patients with a larger uterine volume compared to smaller volumes (OR= 0.998; p=0.03) and patients who anticipated the burden of hysterectomy as being low (low vs. high: OR =5.0; p= 0.08; moderate vs. high: OR=2.56; p=0.23) at baseline were more likely to prefer hysterectomy. No other significant co-variables were found.

Study patients who expressed a preference for hysterectomy at baseline (OR= 9.97; p= 0.0001) and women allocated hysterectomy instead of UAE (OR= 15.1; p=0.0002) were less likely to prefer UAE at 24 months after the procedure (model II).

In the UAE subgroup, patients with lower satisfaction with treatment were less likely to prefer UAE at 24 months compared to those with a high satisfaction (OR=0.02; p=0.002), while clinically successful UAE patients were more likely to prefer UAE at 24 months (OR=38.0; p=0.04) compared to the clinically unsuccessful UAE patients. In the hysterectomy subgroup,

patients with a greater improvement in physical health (higher PCS change score) were less likely to select UAE as the preferred treatment (OR=0.90; p=0.02).

Finally, the effect of (dis)agreement between allocated and baseline preferred treatment on patient's health status and satisfaction was investigated in model III. 59/72 (81.9%) women from the UAE group and 19/63 (30.2%) from the hysterectomy group underwent the preferred treatment. There was neither effect of receiving the preferred treatment in comparison to the non-preferred treatment on the health status (mean difference in SF-36 PCS change score: -1.02; 95%CI: -4.07 to 2.02; p=0.51; mean difference in SF-36 MCS change score: 0.85; 95%CI: -3.67 to 5.37; p=0.71), nor was there any significant effect on satisfaction rating (OR: 0.66; p=0.34). Furthermore, there was no effect between those patients with an outspoken treatment preference at baseline in comparison to those being indifferent, both on health status and on satisfaction (mean difference in SF-36 PCS change score: 0.99; 95%CI: -5.84 to 3.85; p=0.69; mean difference in SF-36 MCS change score: -2.24; 95%CI: -9.23 to 4.74; p=0.69; satisfaction: OR= 3.68; p=0.22).

DISCUSSION

As part of a randomized controlled trial comparing UAE with hysterectomy, we investigated the treatment burden and treatment preferences of these interventions for symptomatic uterine fibroids.

Before treatment, patients anticipated the treatment burden of hysterectomy to be higher than for UAE, especially with regard to hospital stay, post-procedural pain and discomfort. The actually experienced burden after treatment was lower in both groups than expected, especially in the hysterectomy group. Still, patients in both groups reported substantial pain, discomfort and, to a lesser extent, post-procedural complications. This indicates that although UAE is considered a minimally-invasive therapy, the actually experienced pain and discomfort at follow-up should not be underestimated.

Major differences in experienced burden between the two treatments at 6 months were absent, except for the discomfort after treatment (which was higher in the hysterectomy group). The latter is corroborated by the fact that patients after hysterectomy take longer time to recover and resume daily activities[6]. The proportion of patients at baseline that feared the return/persistence of menorrhagia complaints after UAE was substantial (60.4%).The fact that 23.5% of the UAE patients in our study had recurrence or persistence of symptoms illustrates that the fear for unsuccessful treatment by UAE is indeed realistic and that patients are well aware of this [2;5].

In our study we found a higher preference for UAE at baseline in both groups (75% in the UAE group and 63% in the hysterectomy group). At 24 months after treatment, the majority of patients supported the allocated treatment: 73% of the UAE group preferred UAE, while 72% of the hysterectomy patients preferred hysterectomy. This implies that most patients in the UAE group adhered to the baseline preference while most patients in the hysterectomy shifted their preference expressed at baseline. The small number of patients who shifted preference in the UAE group were mostly patients who required a secondary hysterectomy after an unsuccessful UAE treatment. This is in accordance with other reports on preferences for other treatments, which indicate that good outcomes lead to preferences for the allocated treatment [10]. More remarkable is the large shift in preference in the hysterectomy group. One explanation is that hysterectomy had a good clinical outcome for the majority of patients, particularly when the long history of menorrhagia and other complaints and ineffective multiple previous treatments are taken into account. However, we cannot exclude that two other phenomena may have played a role: a learning or experience effect which shows that hysterectomy was experienced less burdensome after treatment than anticipated at baseline which may result in adjustment of prior preferences; and cognitive dissonance reduction, i.e. the psychological phenomenon whereby patients are inclined to emphasize opinions or experiences consistent with their actual behavior and tend to de-emphasize opinions or experiences that contradict these [11]. Furthermore UAE patients were very consistent over time in their preference for UAE even when the success percentages were varied using the "vignettes".

Literature suggest that patients randomized to the non-preferred intervention may suffer from what has been termed "resentful demoralisation', which in turn may lead to worse outcomes either directly (through refusal to adhere to the allocated treatment) or indirectly (through a negative placebo-like effect) [12]. We found that (dis)agreement between allocated and preferred treatment did not have an impact on health-related quality of life and satisfaction, a finding corroborated by others [10;13].

There are some limitations to our study. Firstly, most patients preferred UAE at study entry. The probable cause is selective participation bias: UAE was only available within the study setting, while patients with a strong preference for hysterectomy did not enter the study since hysterectomy was widely available outside the trial as being the standard treatment. The fact that the majority of patients refusing trial participation did so for a strong preference for hysterectomy (58%) (as opposed to 21% for a preference for UAE) is supportive of the supposed mechanism.

Secondly, the most reliable trial design to compare to treatment options would be a double blind randomized controlled trial [14]. For obvious reasons this was not possible in our study.

Hence, preferences at follow-up may have been biased by each patient's own experience with the allocated treatment only.

Finally, we cannot exclude that the treatment and outcome information given prior to study entry and processed in the "vignettes" may have had an impact on preferences. Minor complication rates and secondary hysterectomy rates after clinical failure of UAE were larger than reported in most other (non-randomized) studies. Particularly the uncertainty regarding the secondary hysterectomy rate after clinical failure of UAE was considered a key-parameter. We did not assess the effect of clinical UAE success rates lower than 60%. At the suggested 60% success, 65% of UAE patients still regarded UAE the preferred treatment. The acceptance of low UAE success rates may be influenced by the fact that patients after an unsuccessful UAE procedure can still undergo a hysterectomy or possibly a re-embolization as performed in other studies. Surprisingly, the effect of UAE success rate on preference appears limited since the majority of patients did not shift their preference, a finding highly consistent over time.

This report is part of a randomized controlled trial comparing UAE with hysterectomy, which showed UAE to be a realistic alternative for hysterectomy and which found health-related quality of life at 24 months to be similar after both treatment options [2;4]. Given the equivalence of most of the primary and secondary clinical outcomes and health-related quality of life at two year follow-up, patient's preferences should play a major role in the eventual treatment choice. To enable this choice, patients should be adequately informed about the risks and benefits of both treatment options.

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UTERINE ARTERY EMBOLIZATION **VERSUS** HYSTERECTOMY FOR SYMPTOMATIC UTERINE FIBROIDS

III

VALIDATION AND RELIABILITY

SUBMITTED

12

UTERINE ARTERY EMBOLIZATION OR HYSTERECTOMY IN THE TREATMENT OF UTERINE FIBROIDS? THE IMPACT OF TREATMENT CHOICE ON HEALTH RELATED QUALITY OF LIFE

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ABSTRACT

Introduction

Randomized controlled trials (RCT) are considered to yield the best evidence for comparing treatment effectiveness. By design RCTs provide no insight in the impact of individual choice of treatment on outcome. We compared the health related quality of life (HRQOL) of two treatments (i.e. hysterectomy and uterine artery embolization) for symptomatic uterine fibroids between participants of a RCT and women who refused RCT participation and received the treatment of their preference.

Methods

349 patients were asked to participate in the EMMY trial. 177 agreed to randomization (Randomized group), those who refused randomization formed the Preference group (n=172). At baseline and at 12 months after treatment HRQOL was assessed using the MOS SF-36 Health Survey. HRQOL was expressed as the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. Multiple linear regression analysis was used to test whether the baseline PCS and MCS scores and the PCS and MCS change scores at 12 month follow-up differed between the Randomized and Preference group.

Results

At baseline, the preference group reported significantly better mental health than the randomized group (SF-36 MCS score: 46.1 vs. 41.1, $p<0.0001$). The physical health at baseline did not differ between the preference and randomized group (SF-36 PCS: 43.7 vs. 42.9, $p=0.49$).

At follow-up the difference in mental health between the groups was not significant (mean difference SF-36 MCS: -2.62; 95%CI:-6.23 to 0.98, $p=0.15$). The improvement in physical health was significantly higher in the randomized group (mean difference SF-36 PCS: 5.97; 95%CI: 2.32 to 9.61, $p=0.001$).

At 12 months the change in mental health was negatively influenced by being employed ($\beta=-4.05$; $p=0.03$), but not by being randomized or not ($\beta=-2.93$, $p=0.16$). Physical health was positively influenced by taking part in the randomized trial ($\beta=6.28$, $p=0.002$) and by undergoing a hysterectomy ($\beta=3.58$, $p=0.02$), while a negative effect was found for married patients ($\beta=-3.56$, $p=0.03$).

Conclusion

Patients who selected their own treatment had a better mental health at baseline, while both groups showed equal improvement in mental health at 12 months follow-up. Patients who participated in the RCT showed better improvement in physical health at follow-up than those treated according to their preference.

INTRODUCTION

Although a randomized controlled trial (RCT) is often considered the gold standard in research for determining the efficacy of health interventions, such trials may be vulnerable to 'preference effects'; that is, outcomes may differ depending on whether an individual is randomized to his or her preferred treatment [1]. This occurs especially in trials where patients cannot be blinded for the received treatment. The existence of prior treatment preferences and being able to choose the preferred treatment might have an effect on health related quality of life (HRQOL).

To determine the impact of treatment choice on HRQOL, we compared the HRQOL of patients who participated in a randomized trial to the HRQOL of patients unwilling to enter this trial and who subsequently received the treatment of their own choice. All patients were eligible candidates for the recently conducted EMMY trial which compared hysterectomy and uterine artery embolization (UAE) in the treatment of symptomatic uterine fibroids.

METHODS

STUDY DESIGN

The EMMY trial (EMbolization versus hysterectoMY) is a prospective randomized trial with 34 participating hospitals. Selection of patients was based on the following inclusion criteria: 1) the clinical diagnosis of uterine fibroids as confirmed by ultrasonography; 2) menorrhagia was the predominant complaint; 3) patients were premenopausal and 4) hysterectomy was thought to be the ultimate solution as other treatment options were unsuitable or had failed to provide symptomatic relief. The study was approved by the Central Committee Involving Human Subjects (www.ccmo.nl) and the local ethics committees of all participating hospitals. Eligible patients were informed both verbally and in writing about possible risks and benefits of both procedures. After written informed consent was obtained, patients were randomly assigned (1:1) to hysterectomy or UAE by computerized randomization. These patients composed the randomized group of the present study. All eligible patients who refused participation for various reasons composed the preference group.

In the randomized group of patients, the type of hysterectomy and the route of access were determined by the gynecologist. UAE was performed by an interventional radiologist in accordance with published standards [2;3].

Patients in the preference group were not randomized, but received the treatment of their own choice. The treatment options ranged from either hysterectomy, UAE, myomectomy, GnRH analogues, alternative medicine to no treatment at all.

QUESTIONNAIRES

All patients in the randomized and preference groups were asked to complete a questionnaire at baseline (before randomization) and at 12 months follow-up after the initial procedure. In the randomized group the date of the procedure was known. Patients in the preference group who had completed a baseline questionnaire, received a short inquiry by mail about which treatment(s) they had received and when the treatment(s) had taken place. Patients in the preference group were then asked to complete the follow-up questionnaire 12 months after their intervention. When patients in the preference group had not received any treatment, they were asked to complete the follow-up questionnaire at 12 months after the baseline questionnaire.

The questionnaire consisted of the Medical Outcome Study Short Form-36 (SF-36) health survey which comprises of 36 questions summarized in the following 8 domains of physical and mental functioning: physical functioning, role functioning physical as well as emotional, social functioning, bodily pain, mental health, vitality and general health perceptions [4;5]. The 8 domain scores can be summarized in two summary measures: the physical component summary score (PCS) and the mental component summary score (MCS), which are derived using weighted averages of the individual domain scores [6]. The PCS and MCS provide scores ranging from 0-100 (100 indicating the optimal score).

STATISTICAL ANALYSIS

Data entry was performed using SPSS data entry for Windows 3.0. Analysis was done using SPSS statistical software (version 11.5.1). Study outcomes for the randomized group were analyzed according to the original treatment assignment (intention to treat).

Baseline characteristics of the randomized group were compared to those of the preference group by multiple logistic regression analysis.

Missing values in the SF-36 were calculated according to the scale they were part of. The mean scores of the SF-36 PCS and MCS at baseline and mean change scores at 12 months follow-up were compared between the randomized and the preference group by means of a Student's t-test. The analysis of the PCS and MCS change scores was only based on the data of patients that completed both the baseline questionnaire as well as the 12 months follow-up questionnaire.

To investigate a treatment effect between the randomized and preference group these analyses were re-performed on a subgroup of patients including only the hysterectomy and UAE patients and excluding the 'others' preference group (UAE/randomization; n=73); (UAE/preference; n=7); (hysterectomy/randomization; n=62); (hysterectomy/preference; n=30).

Furthermore univariate linear regression analysis was performed to identify parameters that influenced SF-36 scores at baseline. The following baseline factors were evaluated: age (continuous), ethnicity (black/caucasian/other), marital status (single/married/living apart together-divorced-widow), employment status (employed/unemployed), education level (elementary school/lower secondary school/intermediate-high secondary school/college-university) and participation status (randomized/preference). A similar analysis was performed for the identification of parameters that influenced the SF-36 change score at 12 months. The abovementioned parameters were entered in the multiple linear regression analysis including the following variable: treatment received (hysterectomy/UAE/other chirurgical options/GnRH analogues/alternative medicine/no treatment). Variables with p-values <0.1 in the univariate linear regression analysis were studied in a multiple linear regression analysis. Variables in the multiple linear regression analysis with p-values <0.05 were considered statistically significant. Adjusted R^2 were calculated to evaluate the proportion of variance explained by the model. To look at a treatment effect between the randomized and preference group the multiple regression analyses were re-performed on a subgroup of patients including only the hysterectomy and UAE patients and excluding the 'others' preference group.

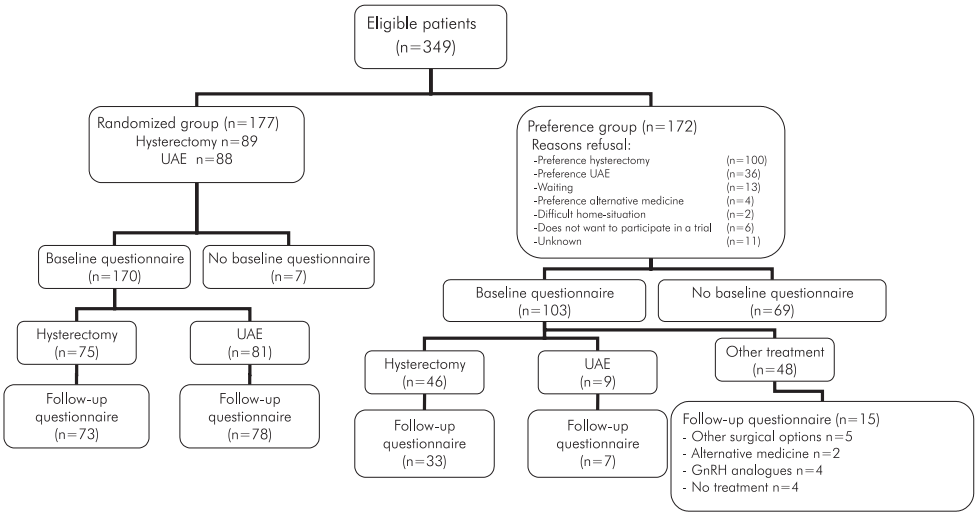
Finally in the preference group, the 'others' subgroup was compared to the hysterectomy and UAE patients.

RESULTS

PARTICIPANTS

Patients were enrolled between March 2002 and February 2004. Twenty eight of the 34 participating hospitals entered patients in the trial. Of 349 eligible patients, 177 agreed to be randomized: 89 were allocated hysterectomy and 88 UAE. In the randomized group 156/177 patients underwent the assigned treatment. The remaining 21/177 (11.9%) refused the allocated treatment and withdrew from the trial altogether. The 172 patients who refused participation formed the preference group. The majority of patients refusing trial participation did so for a strong preference for either hysterectomy (58.1%) or UAE (20.9%), while 20.9% refused for other reasons. They received the treatment of their own preference (Figure 1).

FIGURE 1. Patients flow chart



In the randomization group 155/156 (99.4%) participating patients completed the baseline questionnaire versus 103/172 patients (59.9%) in the preference group. The 12 month follow-up questionnaire was completed by 151/156 (96.8%) in the randomized group, while 75/172 (43.6%) patients in the preference group responded to the short inquiry they received one year after having completed the baseline questionnaire.

Patients in the preference group reported having received the following treatments: hysterectomy (n=46; 61.3%), UAE (n=9; 12.0%), other surgical options like myomectomy (n=7; 9.3%), GnRH analogues or levonorgestrel releasing intrauterine device (n=5; 6.7%), alternative treatment (n=2; 2.7%), or were managed expectantly (n=6, 8.0%). The patients that did not undergo hysterectomy or UAE formed the 'others' subgroup. Of these 75 patients eventually 55 completed the follow-up questionnaire 12 months after treatment: 53.4% of the patients in the preference group who also completed the baseline questionnaire.

The univariate analysis showed that baseline characteristics between the randomized and preference groups differed significantly in terms of ethnicity (more caucasians patients in the preference group) and a better mental health (SF-36 MCS score) in the preference group; educational level (lower secondary school) had a p-value of 0.07 (Table 1). The multiple regression analyses revealed two significant covariables: women in the preference group were significantly higher educated (p=0.04) and they had a better mental health at baseline (p=0.0002).

TABLE 1. Baseline characteristics

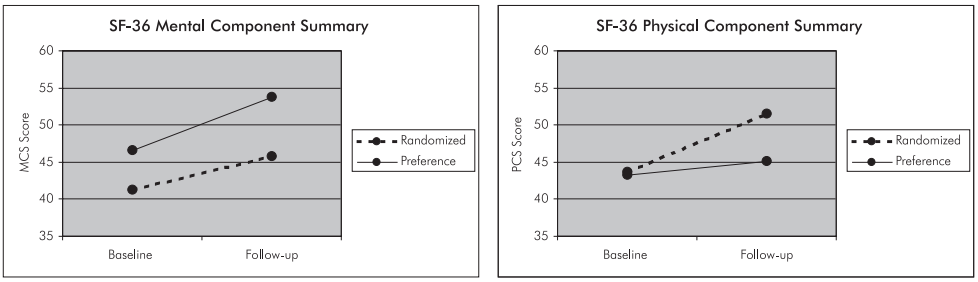
	Randomized group n=170 n (%)	Preference group n=103 n (%)	p-value
Age (years)			0.86
Mean (SD)	45.0 (4.5)	44.9 (4.9)	
Ethnicity			0.01
Black	41 (24.1)	13 (12.6)	
Caucasian	106 (62.4)	82 (79.6)	
Other	23 (13.5)	8 (6.2)	
Marital status			0.3
Single	28 (16.5)	15 (14.6)	
Married	107 (62.9)	72 (69.9)	
Living Apart Together	9 (5.3)	7 (6.8)	
Divorced	24 (14.1)	7 (6.8)	
Widow	2 (1.2)	0 (0)	
Employment status			0.89
Employed	132 (77.6)	78 (75.7)	
Unemployed	38 (22.4)	23 (22.3)	
Educational level			0.07
Elementary school	9 (5.3)	1 (1.0)	
Lower secondary school	60 (35.3)	29 (28.2)	
Interm./ High secondary school	51 (30.0)	26 (25.2)	
College/University	46 (27.0)	41 (39.8)	
MOS SF-36 MCS score			0.0002
Mean	41.1	46.1	
MOS SF-36 PCS score			0.49
Mean	43.7	42.9	
Treatment			0.01
Hysterectomy	75 (44.1)	46 (44.7)	
UAE	81 (47.6)	9 (8.7)	
Other surgical options	0 (0)	7 (6.8)	
GnRH analogues	0 (0)	5 (4.9)	
Alternative treatment	0 (0)	2 (1.9)	
None	0 (0)	6 (5.8)	
Withdrew/Unknown	14 (8.2)	28 (27.2)	

MOS SF-36: Medical Outcome Study Short Form 36; MCS: Mental Component Summary; PCS: Physical Component Summary

HEALTH RELATED QUALITY OF LIFE AT BASELINE

At baseline the preference group showed a significantly better mental health than the randomized group (SF-36 MCS 46.1 versus 41.1; $p<0.0001$ (Figure 2). Physical health, however, did not differ significantly between both groups at baseline (SF-36 PCS randomized group: 43.7 versus preference group: 42.9; $p=0.49$).

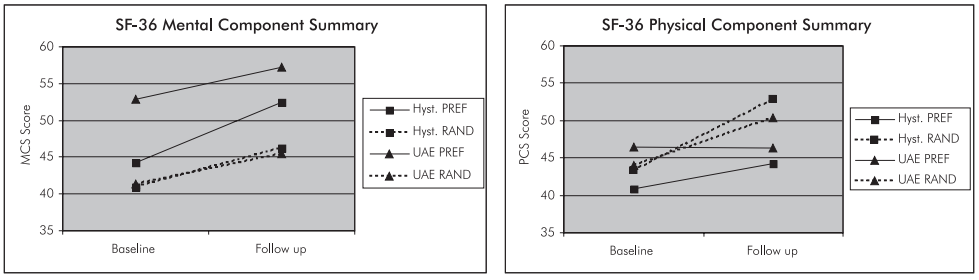
FIGURE 2. SF-36 MCS and PCS at baseline and 12 months follow-up. Comparison between the randomized and preference group



SUBGROUP ANALYSIS AT BASELINE

For the subgroup analysis only the hysterectomy and UAE patients were compared, excluding the "others" subgroup in the preference group. At baseline the hysterectomy patients in the preference group and the randomized group showed no significant differences in mental health (SF-36 MCS score: 44.2 versus 40.9; mean difference: +3.3; 95%CI: -0.54 to 7.21; p=0.09). Similar results were found for physical health of hysterectomy patients between the preference group and the randomization group (SF-36 PCS score: 41.8 versus 43.6; mean difference: -1.72; 95%CI: -5.08 to1.63; p=0.31). In the UAE group there was a significant difference in mental health between the preference and randomized group (SF-36 MCS score: 52.3 versus 41.5, respectively; mean difference: +10.81; 95%CI: 2.95 to 18.68; p=0.008). For the UAE patients no differences were found in physical health between the preference group and randomization group (SF-36 PCS score: 47.2 versus 43.9, mean difference: +3.3; 95%CI: -2.85 to 9.47; p=0.29) (Figure 3).

FIGURE 3. MOS SF-36 MCS and PCS: comparison between various subgroups



PREF: preference group; RAND: randomized group

COVARIABLES AT BASELINE

The multiple linear regression analysis showed that at baseline caucasian patients had a significantly better mental health (SF-36 MCS) (β=4.55; p= 0.001). Also, being employed

was associated with a better mental health at baseline (β=3.89; p=0.0008), while patients that were randomized had a worse mental health (β=-4.28; p=0.001).
For the SF-36 PCS, being single had a negative impact on the physical health (β=-3.88; p=0.003).

HEALTH RELATED QUALITY OF LIFE AT 12 MONTHS FOLLOW-UP

The randomized group improved significantly in both mental and physical health, compared to baseline (SF-36 MCS: +7.85; p <0.0001; SF-36 PCS: + 4.60; p <0.0001). In the preference group, however, only mental health improved compared to baseline, while physical health did not improve significantly (SF-36 MCS: + 1.89; p=0.25; SF-36 PCS: +7.22; p<0.0001) (Figure 2).
Between the randomized and preference group the SF-36 MCS change scores from baseline to 12 months follow-up did not differ (mean difference SF-36 MCS change score: -2.62; 95%CI: -6.23 to 0.98; p=0.15). The randomized group showed a larger improvement in physical health than the preference group (mean difference SF-36 PCS change score: 5.97; 95%CI: 2.32 to 9.61; p=0.001) (Table 2).

SUBGROUP ANALYSIS AT 12 MONTHS FOLLOW-UP

The subgroup analysis at 12 months follow-up was performed including the hysterectomy and UAE patients, but excluding 'the others' subgroup of the preference group.
In the randomized group, the within group analysis showed significant improvements compared to baseline in both mental and physical health at 12 months for both hysterectomy and UAE patients (hysterectomy SF-36 MCS and PCS, mean scores: +5.29 and +9.62; p=0.0002 and p<0.0001, respectively; UAE SF-36 MCS and PCS, mean scores: +4.01 and +6.35; p=0.007 and p<0.0001, respectively).
In the preference group, hysterectomy patients showed significantly improved mental health compared to baseline (SF-36 MCS: +8.27; p=0.0001), while physical health did not improve significantly (SF-36 PCS: +3.54; p=0.13). In the UAE group there was no

TABLE 2. Change in MOS-SF-36 MCS and PCS scores from baseline to 12 months follow up

	Randomized group n=151 Mean difference from baseline	Preference group n=55 Mean difference from baseline	Δ mean (95%CI)	p-value
MOS SF-36 MCS	**4.60**	**7.22**	-2.62 (-6.23 to 0.98)	0.15
MOS SF-36 PCS	**7.85**	1.89	5.97 (2.57 to 9.36)	0.001

The **bold** numbers are significant (p<0.05) increments compared to baseline for the within group analysis.

TABLE 3. Factors associated with HRQOL outcome at baseline and 12 months follow-up

ALL PATIENTS		Beta	95%CI	p-value
Baseline				
MOS SF-36 MCS	Ethnicity (white = 1)	4.55	1.91 to 7.20	0.001
	Employed (yes = 1)	3.89	1.04 to 6.73	0.008
	Randomized (yes = 1)	-4.28	-6.77 to 1.79	0.001
MOS SF-36 PCS	Marital status (single = 1)	-3.88	-6.39 to -1.36	0.003
Change score from baseline to 12 months				
MOS SF-36 MCS	Employed (yes =1)	-4.05	-7.76 to -0.35	0.03
MOS SF-36 PCS	Randomized (yes =1)	6.28	2.93 to 9.63	0.002
	Marital status (married =1)	-3.56	-6.73 to -0.39	0.03
	Received treatment (hysterectomy =1)	3.58	0.61 to 6.55	0.02
HYSTERECTOMY/UAE SUBGROUP *1				
Baseline				
MOS SF-36 MCS	Ethnicity (white = 1)	5.80	2.78 to 8.84	0.0002
	Employed (yes = 1)	3.78	0.48 to 7.08	0.03
MOS SF-36 PCS	Marital status (single = 1)	-4.43	-6.99 to -1.87	0.001
	Ethnicity (other = 1)	-4.12	-7.87 to -3.77	0.03
Change score from baseline to 12 months				
MOS SF-36 MCS	Employed (yes =1)	-5.00	-8.85 to -1.17	0.011
MOS SF-36 PCS	Randomized (yes =1)	5.11	1.39 to 8.84	0.007
	Marital status (married =1)	-10.32	-18.73 to -1.91	0.02
	Educational level (elementary school =1)	-4.0	-7.37 to -0.73	0.02

*1 Excluding the 'others' group in the preference group

significant difference in mental or physical health (SF-36 MCS: +4.38; p=0.21; SF-36 PCS: -0.21; p=0.95) (Table 4).

For the hysterectomy patients, the change scores for the SF-36 PCS were significantly higher in randomized hysterectomy patients compared to the preference group (mean difference in SF-36 PCS change score: +6.08; 95%CI: 1.22 to 10.95; p=0.02). For the UAE group the SF-36 PCS change score was not significantly different between the randomized and preference group (mean difference SF-36 PCS change score: 6.56; 95%CI: -0.83 to 13.94; p=0.08).

Other comparisons regarding the SF-36 MCS change scores were not significant (mean difference SF-36 MCS change score; hysterectomy: -2.98: 95%CI: -7.56 to 1.60; p=0.20; UAE: 0.37; 95%CI: 9.94 to 9.21; p=0.94) (Table 4).

No significant differences were observed between the hysterectomy/UAE group and the "others" group of the preference group with regard to the baseline SF-36 MCS (mean difference: -1.48; 95%CI: -4.95 to1.99; p=0.40) and PCS (mean difference: -0.54; 95%CI: -4.44 to3.36; p=0.79). At 12 months follow-up no differences were found for the

TABLE 4. Change in MOS SF-36 MCS and PCS scores randomized hysterectomy/UAE group versus preference hysterectomy/UAE group from baseline to 12 months follow-up

	Randomized hysterectomy group n=73 Mean difference from baseline	Preference hysterectomy group n=33 Mean difference from baseline	meanΔ (95%CI)	p-value
MOS SF-36 MCS	**5.29**	**8.27**	-2.98 (-7.56 to 1.60)	0.20
MOS SF-36 PCS	**9.62**	3.54	6.08 (1.22 to 10.95)	0.02
	Randomized UAE group n=78 Mean difference from baseline	Preference UAE group n=7 Mean difference from baseline	meanΔ (95%CI)	p-value
MOS SF-36 MCS	**4.01**	4.38	0.37 (-9.94 to 9.21)	0.94
MOS SF-36 PCS	**6.35**	-0.21	6.56 (-0.83 to 13.94)	0.08

The **bold** numbers are significant ($p<0.05$) increments compared to baseline for the within group analysis.

SF-36 MCS change scores (mean difference: +3.6; 95%CI: -3.78 to 11.04; p=0.33) and SF-36 PCS change score (mean difference: +1.19; 95%CI: -4.92 to 7.31; p=0.70).

COVARIABLES AT 12 MONTHS FOLLOW-UP

Only one factor, i.e. being unemployed, was associated with improved mental health at 12 months follow-up (SF-36 MCS change score; $\beta=4.05$; p= 0.03). Being randomized or not did not influence the mental health ($\beta=-2.93$, p=beta, p=0.16).

Two factors were associated with improved physical health after treatment: participating in the randomized group (SF-36 PCS change score: $\beta=6.28$; p=0.002) and receiving hysterectomy as treatment ($\beta=3.58$; p= 0.02). Physical health was negatively influenced in women who were married (SF-36 PCS change score: $\beta=-3.56$; p= 0.03).

DISCUSSION

In this paper we studied the impact of treatment choice on mental and physical quality of life. We compared a randomized group of women who participated in the randomized EMMY trial with a preference group of women who declined trial participation, at baseline and at 12 months follow-up. All patients were eligible candidates for the recently conducted EMMY trial, a RCT comparing hysterectomy and uterine artery embolization (UAE) in the treatment of symptomatic uterine fibroids.

Comparing baseline HRQOL between the randomized and preference group showed that the preference group, especially the UAE patients, had a significantly better mental health

than randomized patients. The probable explanation is that non-participants had a strong treatment preference for one treatment or the other, as in fact the reasons for refusing trial participation reveal. Patients with clear preferences may have better feelings of self control and are conscious of what they want-and do not want.

At 12 months follow-up, mental health had increased in both groups, but the increase was significantly higher in the preference group than in the randomized group. This might be attributed to the fact that these women indeed received the treatment they preferred. This probably adds to the feeling of higher self-esteem [1], which may be regarded as the biasing effect from the psychological phenomenon of "cognitive dissonance reduction" [7]; patient's tendency to believe that the treatment selected was indeed the best option, thus resulting in an improved mental health experience.

At 12 months follow-up, the randomized group showed the largest improvement in physical health. Physical health, however, did not improve in the preference group, especially not in women opting for UAE. This finding is not surprising in view of the fact that a substantial proportion of patients from the preference group (n=48) received less rigorous treatment options than hysterectomy or UAE while hysterectomy was indicated. But even after exclusion of this 'undertreated' subgroup, the randomized group showed better improvement in physical health than those treated according to their preference.

Apparently physical health improves significantly more when patients participate in a trial. Another variable that contributed to better physical health were receiving a hysterectomy (β=6.28; p=0.002), while, surprisingly, being married negatively influenced the physical health (β=-3.56; p=0.03).

Our findings are in contrast to a recently conducted systematic review on the effect of choice on clinical outcome concluded that there were no differences in clinical outcome between randomized and preference groups [8].

The most apparent baseline characteristic that positively influenced HRQOL at baseline was ethnicity. Caucasian patients had a better HRQOL at baseline and 12 months follow-up. It has been reported that fibroids in black women occur more commonly, are larger, and result in more severe symptoms [9]. Black women have also been reported to be more inclined to report pain and bleeding in comparison to caucasian women [10;11]. The proportion of caucasian women was significantly higher in the preference group. This might explain why at baseline, mental health in the randomized group was reported worse than in the preference group, and also why being caucasian was associated with a higher HRQOL at baseline. An earlier study showed higher educated women to have higher HRQOL and to be less prone to depression [12]. This may have attributed to the finding that more patients in the preference group had a higher educational level, albeit not significantly so. Another observation from the

literature shows lower educated women to be at a greater risk of undergoing a hysterectomy. In a study by Harlow et al. only one in five highly educated women compared with four of five less educated women (high school or less) initially accepted hysterectomy as the treatment of choice [13]. The lower educated women in this study were more likely to be randomized and therefore to accept a hysterectomy, which is an effective treatment for their complaints.

Some limitations of this study need to be mentioned.

Firstly, the number of patients that were 'analyzable' in the preference group was relatively small compared to the randomized group (32% versus 85%), possibly biasing the outcomes of the preference group. Secondly in this study other treatments than UAE or hysterectomy were performed in the preference group, making the groups not completely comparable. However, when we excluded patients that received another treatment than hysterectomy or UAE, the results in HRQOL were similar.

In conclusion, this study demonstrates that patients who selected their own treatment had a better mental health at baseline, while both the randomized and preference group showed improved mental health at 12 months follow-up. At 12 months no differences in mental health were found between the groups. Patients who participated in the RCT showed better improvement in physical health at follow-up than those treated according to their preference.

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MR REPRODUCIBILITY IN THE ASSESSMENT OF UTERINE FIBROIDS FOR PATIENTS SCHEDULED FOR UTERINE ARTERY EMBOLIZATION

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ABSTRACT

Purpose

Magnetic resonance imaging (MRI) is increasingly applied in the evaluation of uterine fibroids. However, little is known about the reproducibility of MRI in the assessment of uterine fibroids. This study evaluates the inter- and intra-observer variation in the assessment of the uterine fibroids and concomitant adenomyosis in women, scheduled for uterine artery embolization (UAE).

Methods

Forty patients (mean age: 44.5 years) with symptomatic uterine fibroids who were scheduled for UAE underwent T_1- and T_2-weighted MR imaging. To study inter- and intra-observer agreement 40 MR images were evaluated independently by two observers and re-evaluated by both observers 4 months later. Inter- and intra-observer agreement was calculated using Cohen's kappa statistic (κ) and intraclass correlation coefficient (ICC) for categorical and continuous variables, respectively.

Results

Inter-observer agreement of uterine volumes (κ=0.99; p<0.0001), dominant fibroid volumes (κ=0.98; p=<0.0001) and the number of fibroids (κ=0.88; 95%CI: 0.77-0.93; p<0.0001) was excellent. For the T_1- and T_2 signal-intensity of the dominant fibroid there was a good agreement between the observers (87%; 95%CI: 71.9-95.6) and the intra-observer agreement for observer A was good (95%; 95%CI: 83.1-99.4) and moderate for observer B (κ=0.47). The inter-observer agreement with respect to the presence of adenomyosis was good (κ=0.62; p<0.0001), while both intra-observer agreements were excellent (observer A: κ=0.87; p=0.01 and observer B: κ=0.85; p<0.0001).

Conclusion

MR imaging criteria used for the selection of suitable UAE patients show a good inter- and intra-observer reproducibility.

INTRODUCTION

Magnetic resonance imaging (MRI) is increasingly applied for the evaluation of uterine fibroids before and treatment effectiveness after Uterine Artery Embolization (UAE). MRI is thought to be very useful in assessing the eligibility of UAE patients, especially in comparison to ultrasound (US) imaging which may be hampered by the mere size of the fibroid uterus [1]. A previous study indicated that MR imaging should be considered in all patients with presumed fibroids, because it would significantly alter the diagnosis and treatment plans of interventional radiologists [2]. Various findings on MR imaging are thought to be of special interest in determining the suitability of patients for UAE treatment, i.e. size of the uterus and fibroids, number and location of fibroids, presence of pedunculated fibroids, signal intensity on T_1- and T_2-weighted images, and the presence of any concomitant adenomyosis. Until now only one study has investigated some of these items in an inter-observer study [3].

This study aims to evaluate inter- and intra-observer agreement for MRI parameters which may be of clinical importance in planning UAE in women with uterine fibroid disease.

METHODS

PATIENTS

Forty patients were recruited from 9 of the 34 participating hospitals in the multicentre, randomized trial (EMMY-trial) which compares uterine artery embolization (UAE) with hysterectomy in women with fibroid disease [4;5]. Patients were included if: 1) the clinical diagnosis of uterine fibroids had been confirmed by ultrasonography, 2) menorrhagia was the predominant complaint among other probably fibroid related signs and symptoms, 3) hysterectomy was thought to be the ultimate solution and other treatment options were unsuitable or had failed to provide symptomatic relief, 4) they were premenopausal, 4) preservation of the uterus was not warranted for future pregnancy, 5) the following disorders were absent: renal failure (creatinine >150 mmol/L), active pelvic infection, clotting disorders, allergy to contrast fluid, (suspected) uterine malignancy, submucosal fibroids protruding by >50% within the uterine cavity or pedunculated abdominal fibroids.

Of the 81 patients who underwent MR imaging as part of the diagnostic work-up prior to the UAE procedure, 40 patients had available digital images. Because patients subsequently underwent UAE and consequently did not receive a hysterectomy, no histopathological reports were obtained to validate the measurements. Written informed consent was obtained

in all patients. The study was approved by the Central Committee Involving Human Subjects (www.ccmo.nl) and by the local ethics committees of all participating hospitals.

IMAGING TECHNIQUE

MR imaging was performed using different brands of 1.0 T (n=7) or 1.5 T (n=33) MRI scanners all equipped with a phased array body coil. Most scans were performed on a 1.5 T MR unit (General Electric Horizon Echospeed, General Electric, Milwaukee, Ill). Sagittal T_1-weighted TSE images were performed as well as T_2-weighted images in sagittal, axial and coronal direction with slice orientation perpendicular and parallel to the long axis of the uterine cavity.

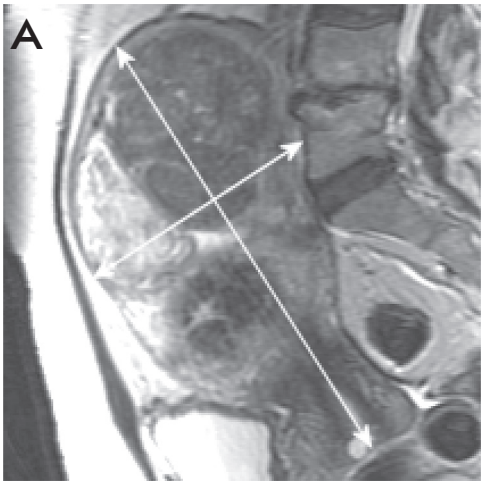
The pelvic MRI was performed by using the following T_2-weighted TSE sequences: TR 6000 ms, TE 96 ms, field of view 300 x 300 cm, imaging matrix 224 x 512 (sagittal and transversal/oblique), 7 mm slice thickness and 0.7 mm interslice gap. The use of contrast was optional in this trial and administered in 10 of the 40 patients. This number was too small to allow further analysis.

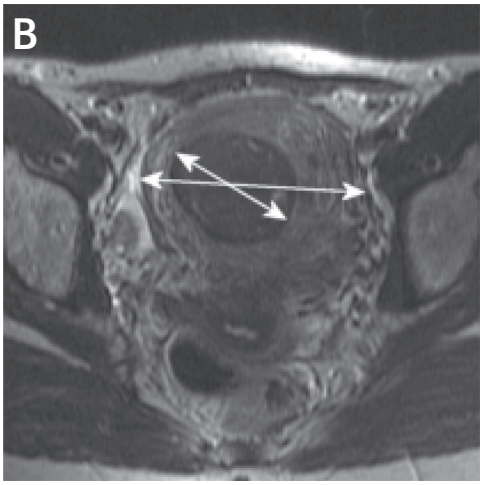
IMAGE ANALYSIS

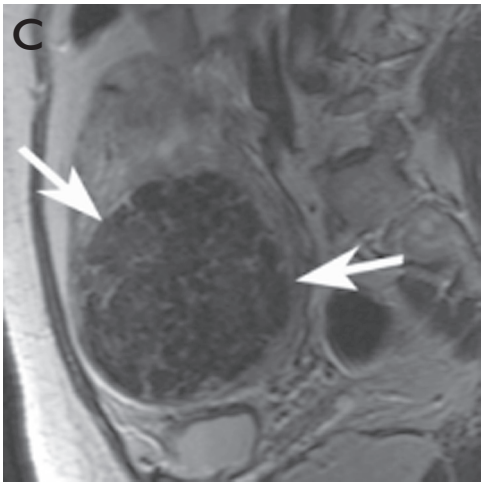
One radiologist and one senior resident in radiology (observer A [*AS*] and B [*AM*]) both with ample experience in abdominal MR imaging, working in different hospitals, read the MR images. Both observers had a training session where instructions on the evaluation of the MR images were provided. Both observers independently evaluated all 40 MR images. On a second occasion, 4 months after the first reading, both observers independently evaluated all MR images once again in a random order to avoid recall bias. Both observers were blinded for their own and each other's results. They were aware, however, that patients were participants of the Emmy trial and that, obviously, uterine fibroids were to be expected.

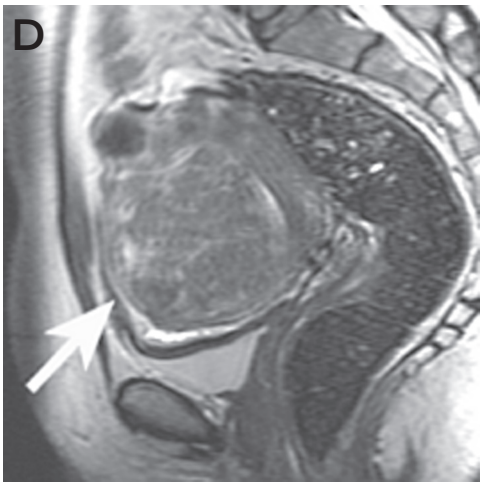
The MR images were examined on a workstation with viewing software (IMPAX SP4 SU4 DS3000, AGFA, Mortsel, Belgium).

Both observers evaluated and recorded the overall quality of the images as good, moderate or poor. The position of the uterus was classified as either anteflexed, in a straight position or retroflexed. The total number of fibroids was recorded. The largest fibroid was indicated as the dominant fibroid. The homogeneity of the dominant fibroid was graded as homogenous or inhomogeneous. The location of the dominant fibroid was defined as being either submucosal (the epicentre of the fibroid is closer to the uterine cavity than to the myometrium), intramural or subserosal (the epicenter of the fibroid is closer to the abdominal cavity than to the myometrium). The presence (yes/no), number (total) and location (subserosal, submucosal or both) of pedunculated fibroids (diameter of the stalk of the fibroid was < 50% of the largest









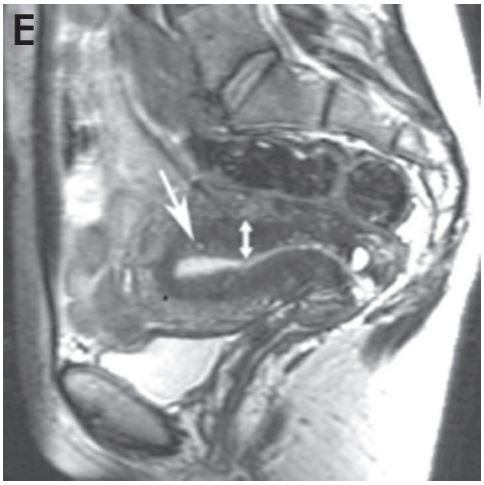


FIGURE 1A: Sagittal T_2-weighted MR image; uterus with 3 intramural fibroids: measurement of the largest longitudinal (long arrow) and anterior-posterior distance of the uterus.

FIGURE 1B: Transversal T_2-weighted MR image: measurement of the largest transverse distance of the uterus (long arrow) and the dominant uterine fibroid (small arrow).

FIGURE 1C: Sagittal T_2-weighted MR image; image of a hypointens intramural uterine fibroid (2 arrows).

Figure 1D: Sagittal T2-weighted MR image; image of an isointens intramural uterine fibroid (arrow).

FIGURE 1E: Sagittal T_2-weighted MR image: image of adenomyosis of the uterus. The thickness of the junctional zone is indicated by the double arrow, the myometrial high signal foci is indicated by the arrow.

diameter of the fibroid), which were not regarded as the dominant fibroid, were recorded. Uterine and dominant fibroid volumes were determined by measuring the maximum linear dimension in three planes (i.e. longitudinal (D1), anterior-posterior (D2), and transverse (D3)) and applying the ellipsoid formula (volume = D1 × D2 × D3 × 0.5233) [6]. The longitudinal and anterior-posterior distances were measured in the sagittal plane (Figure1A), while the transverse diameter was measured in the transverse or coronal plane (Figure 1B). The cervix was excluded in the measurement of the uterine volume. The signal intensity of the dominant fibroid was recorded at the T_1- and T_2-weighted MR images and was classified as predominantly hypointens (Figure1C), isointens (Figure1D) or hyperintens (no example could be provided) compared to normal myometrial tissue.

Since adenomyosis is a well recognized differential diagnosis in women with enlarged uteri and/or menstrual disorders which may cause clinical failures of UAE for fibroid disease, we also assessed inter- and intra-observer agreement on the presence of any concomitant adenomyosis.

Adenomyosis was considered present by the observers whenever a diffuse or focal widening of the junctional zone >5 mm was present [7;8]. The maximal thickness of the junctional zone was measured. The presence of myometrial high-signal foci was considered ancillary evidence of adenomyosis (Figure 1E).

STATISTICAL ANALYSIS

Data entry was performed using SPSS data entry for Windows 3.0. All data entries were visually double checked by an independent second investigator. Analysis was done using SPSS statistical software (version 11.5.1).

Cohen's unweighted kappa statistic (κ) with 95% confidence intervals (95%CI) was used to express inter-observer and intra-observer agreement for categorical MRI parameters. Inter-and intra-observer reproducibility for continuous variables (i.e. uterine and dominant volumes, number of (pedunculated) fibroids, thickness of junctional zone), were assessed with the intraclass correlation coefficient (ICC) using two way mixed analysis of variance (consistency type). The kappa values and intraclass correlation coefficients were interpreted as follows: <0.20: poor agreement; 0.20-0.40: fair agreement; 0.41-0.60: moderate agreement; 0.61-0.80, good agreement; 0.81-1.00, excellent agreement [9]. A two-tailed p-value < 0.05 was considered statistically significant. Whenever kappa values could not be calculated due to the fact that two or more categories of a MRI parameter were never scored by the two observers, percentages of full agreement with 95%CI were calculated.

RESULTS

PATIENTS

Between March 2002 and February 2004, all 40 patients recruited in 9 hospitals were included and underwent MR imaging prior to the UAE procedure. Patients' mean age was 44.5 years (range 38-54 years). Table 1 depicts the results of the first evaluation of both observers. Overall the quality of the images was moderate to good. For both reviewers the position of the uterus was predominately in anteflexion and the location of the dominant fibroid was mostly intramural. The presence of any peduculated fibroid(s) was reported by observer A as 13/40 (32.5%) and observer B as 12/39 (30.8%). The majority of dominant fibroids had an isointens signal intensity on T_1-weighted images and a hypointens signal intensity on T_2-weighted images. The mean number of fibroids observed was respectively 8 and 7 for observer A and B. Adenomyosis was observed in 10 patients by observer A and 17 patients by B.

INTER-OBSERVER REPRODUCIBILITY

Between observer agreement was excellent for the calculation of uterine (κ = 0.99) and dominant fibroid volumes (ICC = 0.98), number of fibroid(s) (ICC = 0.88) and the presence of pedunculated fibroid(s) (κ = 0.82) (Table 2). Good agreement between the observers was found for the location of the dominant fibroid (κ = 0.80), presence of any concomitant adenomyosis (κ = 0.62), thickness of the junctional zone (ICC = 0.62) and signal-intensity of the dominant fibroid on T_1- and T_2-weighted images (respectively κ = 0.70 and 33/38 [87%]; 95%CI: 71.9 to 95.6). (Percentages of full agreement are reported since the kappa values for the T_2-signal-intensity could not be calculated). Inter-observer agreement was moderate for the position of the uterus (κ = 0.52), location (κ = 0.54) and number of pedunculated fibroid(s) (ICC = 0.59) and fair agreement for the homogeneity of the dominant fibroid (κ = 0.28). Due to small numbers, no definite conclusion can be drawn for the presence of high-signal-intensity foci (κ = 0.58; p=0.07).

INTRA-OBSERVER REPRODUCIBILITY

For observer A the intra-observer agreement was excellent for both the uterine (ICC = 0.995) and dominant fibroid volumes (ICC = 0.98), the number (ICC = 0.92), presence (κ = 1.0) and location of (pedunculated) fibroids (κ = 1.0), the position of the uterus (κ = 0.94), the homogeneity of the dominant fibroid and the presence of adenomyosis (Table 3). Good agreement between the first and second reading of observer A was found for signal intensity of the dominant fibroid on the T_1- and T_2-weighted MR images (respectively, κ =

TABLE 1. Parameter outcome of the first evaluation from Observer A and B

	Observer A n (%)	Observer B n (%)
Quality MR image *1		
Good	27 (67.5)	26 (66.7)
Moderate	13 (32.5)	13 (33.3)
Poor	0 (0)	0 (0)
Position of the uterus		
Anteflexion	30 (75.0)	23 (57.5)
Straight position	5 (12.5)	10 (25.0)
Retroflexion	5 (12.5)	7 (17.5)
Uterine volume *2		
Mean (SD)	559.4 (630.5)	620.2 (681.9)
Median (range)	360.7 (51-3056)	382.3 (38-3267)
Dominant fibroid volume *3		
Mean (SD)	170.9 (229.5)	162.6 (213.7)
Median (range)	80.9 (4-1014)	47.8 (3-897)
Location of dominant fibroid *3		
Submucosal	10 (25.0)	13 (34.2)
Intramural	26 (65.0)	22 (57.9)
Subserosal	4 (10.0)	3 (7.9)
Signal intensity dominant fibroid (T1) *4/*5		
Hypointens	2 (5.3)	5 (13.9)
Isointens	34 (89.5)	29 (80.6)
Hyperintens	2 (5.3)	2 (5.6)
Signal intensity dominant fibroid (T2) *3		
Hypointens	40 (100.0)	33 (86.8)
Isointens	0 (0)	5 (13.2)
Hyperintens	0 (0)	0 (0)
Homogeneity of dominant fibroid *3		
Homogeneous	15 (37.5)	5 (13.2)
Inhomogeneous	25 (62.5)	33 (86.8)
Number of fibroids		
Mean (SD)	8.0 (6.5)	7.0 (6.7)
Median (range)	6 (1-27)	4.5 (0-30)
Presence of pedunculated fibroid(s) *1*6		
Yes	13 (32.5)	12 (30.8)
Number of pedunculated fibroid(s) *7		
Mean (SD)	2.3 (1.4)	1.8 (1.0)
Median (range)	2 (1-5)	1.5 (1-4)
Location of pedunculated fibroid(s) *7		
Submucosal	7 (53.8)	5 (41.7)
Subserosal	5 (38.5)	6 (50.0)
Submucosal and subserosal	1 (7.7)	1 (8.3)
Presence of adenomyosis		
Yes	10 (25.0)	17 (42.5)
Thickness of junctional zone (mm) *5/*8		
Mean (SD)	14.1 (4.1)	12.0 (3.4)
Median (range)	13 (10-23)	11 (8-19)
Presence of high-signal-intensity foci *8		
Yes	4 (10.0)	8 (20.0)

*1 Observer B: 1 missing; *2 Observer A: 1 missing; *3 Observer B: 2 missing ;*4 Observer A: 2 missing; *5 Observer B: 4 missing ;*6 non-dominant fibroid; *7 if a pedunculated fibroid was present; *8 if adenomyosis was present

TABLE 2. Inter-observer agreement of MRI (Observer A versus Observer B)

Variable	κ	95%CI	p-value
Quality MR image	0.42	0.12 to 0.72	0.008
Position of the uterus	0.52	0.26 to 0.77	<0.0001
Location of dominant fibroid	0.80	0.63 to 0.97	<0.0001
Homogeneity of dominant fibroid	0.28	0.00 to 0.67	0.03
Presence of pedunculated fibroid(s)	0.82	0.63 to 1.00	<0.0001
Location of pedunculated fibroid(s)	0.54	0.10 to 0.98	0.02
Signal intensity dominant fibroid (T1)	0.70	0.36 to 1.00	<0.0001
Signal intensity dominant fibroid (T2)	*1		
Presence of adenomyosis	0.62	0.37 to 0.87	<0.0001
Presence of high-signal-intensity foci	0.58	0.07 to 1.00	0.07
	ICC		
Volume uterus	0.99	0.97 to 0.99	<0.0001
Volume dominant fibroid	0.98	0.96 to 0.99	<0.0001
Number of fibroid(s)	0.88	0.77 to 0.93	<0.0001
Number of pedunculated fibroid(s)	0.59	0.02 to 0.87	0.02
Thickness of junctional zone	0.62	0.00 to 0.90	0.03

κ = kappa, 95%CI = 95% confidence interval, ICC = intraclass correlation coefficient, p-value: significance level; *1 kappa values could not be calculated; % are given in text

0.73 and 38/40 [95%]; 95%CI: 71.9 to 95.6). (Again kappa values could not be calculated for the T_2-signal-intensity; percentages of full agreement are reported instead). Agreement between both readings was moderate for the presence of high-signal intensity foci (κ = 0.58; p=0.07). Although the agreement for the presence of adenomyosis was excellent, the kappa value for the thickness of the junctional zone was poor (ICC = 0.19; p=0.30).

For observer B, intra-observer agreement was excellent for the uterine (ICC = 0.98) and dominant fibroid volumes (ICC = 0.97), the presence (κ = 0.87), number (ICC = 0.84) and location of pedunculated fibroids (κ = 0.82) and the presence of adenomyosis (κ = 0.85). The agreement on the presence of high-signal-intensity foci (κ = 0.84) was also very good, but agreement on the junctional zone thickness was just fair (ICC = 0.55). Good agreement between the first and second reading by observer B was found for the position of the uterus (κ = 0.73). Agreement between both readings was moderate for the number of fibroids (ICC = 0.58), location (κ = 0.65) and homogeneity of dominant fibroid (κ = 0.54), signal-intensity on T_2-weighted MR images (κ = 0.47). Agreement was fair for observer B for the signal intensity on T_1-weighted images (κ = 0.22).

TABLE 3. Intra-observer agreement of MRI

Variable	Observer	κ	95%CI	p-value
Quality MR image	A	0.27	0.00 to 0.64	0.05
	B	0.45	0.14 to 0.76	0.004
Position of the uterus	A	0.94	0.83 to 1.00	<0.0001
	B	0.73	0.53 to 0.93	<0.0001
Location of dominant fibroid	A	0.80	0.63 to 0.97	<0.0001
	B	0.65	0.44 to 0.86	<0.0001
Homogeneity of dominant fibroid	A	0.83	0.65 to 1.00	<0.0001
	B	0.54	0.18 to 0.90	0.001
Presence of pedunculated fibroid(s)	A	1.0	-	<0.0001
	B	0.87	0.70 to 1.00	<0.0001
Location of pedunculated fibroid(s)	A	1.0	-	<0.0001
	B	0.82	0.51 to 1.00	0.003
Signal intensity dominant fibroid (T_1)	A	0.73	0.37 to 1.00	<0.0001
	B	0.22	0.08 to 0.72	0.02
Signal intensity dominant fibroid (T_2)	A	*1	-	-
	B	0.47	0.05 to 0.89	<0.0001
Presence of adenomyosis	A	0.87	0.69 to 1.00	0.01
	B	0.85	0.68 to 1.00	<0.0001
Presence of high-signal-intensity foci	A	0.58	0.07 to 1.00	0.07
	B	0.84	0.63 to 1.00	<0.0001
		ICC		
Volume uterus	A	0.995	0.99 to 0.997	<0.0001
	B	0.98	0.97 to 0.99	<0.0001
Volume dominant fibroid	A	0.98	0.96 to 0.99	<0.0001
	B	0.97	0.94 to 0.98	<0.0001
Number of fibroid(s)	A	0.92	0.85 to 0.96	<0.0001
	B	0.58	0.33 to 0.75	<0.0001
Number of pedunculated fibroid(s)	A	0.84	0.55 to 0.95	0.0001
	B	0.84	0.49 to 0.96	0.0006
Thickness of junctional zone	A	0.19	0.00 to 0.73	0.30
	B	0.55	0.00 to 0.84	0.03

κ = kappa, 95%CI = 95% confidence interval, ICC = intraclass correlation coefficient, p-value: significance level; *1 kappa values could not be calculated; % are given in text

DISCUSSION

We found good to excellent agreement between and within the observers for the uterine and dominant fibroid volumes, number of fibroids (except for observer B), location of dominant fibroid, position of the uterus (except for the inter-observer agreement), the signal-intensity on T_1- and T_2-weighted MR images (except for observer B), the presence of pedunculated fibroids and the presence of adenomyosis. Especially these MRI parameters seem to be of value in the diagnostic work-up of patients with uterine fibroids.

Our study has certain limitations. Firstly, MR images were performed on a variety of MR scanners. Given our favorable results, heterogeneity of MR scanners appears no major problem, and probably increases the generalizability of our findings. Secondly, recent papers use a thickening of the junctional zone of 12-15 mm as a cut-off point for the diagnosis of adenomyosis, which obviously differs from the older definition we used (> 5 mm) [8]. In our study population the median junctional zone was 13 mm (range: 10-23 mm) for observer A and 11 mm (range: 8-19 mm) for observer B, thus indicating that our results comply with the new definition for adenomyosis. It seems most probable, therefore, that our kappa value would also apply to recent cut-off value.

Various studies found that MRI was superior to ultrasound in establishing the number and exact location of fibroids [1;10-12]. This is important, since these findings play an important role in the identification of eligible patients for undergoing UAE or for planning surgical procedures, especially myomectomy [13]. One study which compared MRI, transvaginal ultrasound and pathological examination reported that the performance of ultrasound was significantly poorer for fibroids larger than 375 ml, while the accuracy of MRI was independent of the uterine volume [1]. Location of a fibroid can play a role in the identification of suitable patients for UAE, since an earlier study indicated that submucosal fibroids had a higher chance of volume reduction after UAE [13]. Pedunculated subserosal fibroids are generally recognized as relative contraindication for the use of UAE [14]. This contraindication stems from the potential hazard for pedunculated subserosal fibroids to separate from the uterus due to stalk necrosis, which may result in serious complications [15;16].

Scores for signal intensity of the dominant fibroid in our study were variable: the inter-observer agreement was good for signal intensity on T_1- and T_2-weighted images, while the intra-observer agreement varied from good for observer A to fair to moderate for observer B. Signal-intensity on MR imaging may be an indicator for treatment success of UAE. A high T_1-weighted signal-intensity at baseline was found to be a predictor for a poor response in terms of reduced fibroid volume and vascularity, as was a large uterus [3;17], while a high signal-intensity on T_2-weighted images was found to be predictive of increased uterine volume reduction compared to those with low signal-intensity at baseline [17-19].

Only one earlier study has investigated the inter-observer agreement between three observers for various characteristics on MR images in women with fibroid disease. That study observed excellent kappa values for identifying the location of the dominant fibroid, as well as for signal-intensity on T_1-weighted images (κ = 0.80-0.95), T_2-weighted images (κ = 0.92-1.0), T_2-weighted heterogeneity (κ = 0.81-0.92) and gadolinium enhancement (κ = 0.96-1.0) [3]. Our data confirmed these observations for the location of the dominant fibroid,

except for the kappa values of observer B, which showed less agreement for signal-intensity on T_1- and T_2-weighted images.

In the literature, opinions differ widely on the question as to whether adenomyosis should be treated with UAE. Some studies have reported encouraging short-term clinical results [20-22], while one case report concluded that concomitant adenomyosis was the main reason for clinical failure of UAE in women with fibroid disease [23]. One larger study showed that despite encouraging short-term results of UAE in treating adenomyosis, mid-term results were rather disappointing, with only 55% of patients showing clinical improvement after 2 years [24].

Thus, it seems important to distinguish between adenomyosis and fibroid disease especially in patients scheduled for UAE, but this can be quite challenging, mainly because both uterine abnormalities are assumed to coexist in 20% of patients [25] and cause similar symptoms of abnormal uterine bleeding and dysmenorrhoea. Most authors recommend the use of MR imaging, particularly in patients with associated gynecologic disorders. The sensitivity and specificity of MR imaging in diagnosing adenomyosis range from 77.5% to 89% and from 67% and 92.5% [8;26;27]. One study compared MRI findings with histopathologic findings as a gold standard, and concluded that MR imaging is highly accurate in distinguishing between adenomyosis and fibroids in patients with enlarged uteri [28]. Using a standardized MR definition for adenomyosis, we found inter-and intra-observer agreement to be good to excellent.

In conclusion, MR imaging criteria used for the selection of suitable UAE patients showed a good inter- and intra-observer reproducibility, thereby confirming that commonly used MR imaging prior to UAE is reliable.

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SUBMITTED

14

THE ESTIMATION OF UTERINE VOLUME: A COMPARISON OF ULTRASOUND AND BIMANUAL EXAMINATION VERSUS ACTUAL VOLUME AT HYSTERECTOMY AND MRI

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ABSTRACT

Objective

To compare the accuracy in determining Uterine Volume (UV) of bimanual examination ('Clinical UV') and ultrasound ('Ultrasound UV'), with 'True UV' obtained from pathology reports and Magnetic Resonance Imaging ('MRI UV').

Methods

Patients were pre-menopausal women with a symptomatic fibroid uterus undergoing either uterine artery embolization or hysterectomy. Clinical UV and Ultrasound UV versus True UV were compared in terms of Intra Class Correlations (ICC) and mean difference in UV. Comparisons of Clinical UV versus Ultrasound UV versus MRI UV were expressed in terms of ICC and Bland-Altman's Limits of Agreement (LOA).

Results

Correlation between Ultrasound UV and True UV was good (ICC=0.64, mean difference: +62 grams, 95%CI: -49 to 172) and moderate between Clinical UV and True UV (ICC=0.58, mean difference: +117 grams, 95%CI: 17 to 217). Agreement between MRI and Ultrasound UV was good (ICC=0.75; LOA: ±713 grams), between MRI UV and Clinical UV also good (ICC =0.67; LOA: ±765 grams) and between Clinical UV and Ultrasound UV moderate (ICC=0.55; LOA: ±676 grams). Clinical UV was significantly higher than Ultrasound UV (mean: +70 grams, 95%CI: 36 to 103; p=0.0001).

Conclusion

Ultrasound showed a better correlation with True UV than Clinical examination. Ultrasound UV and MRI UV show the best correlation. Since ultrasound is more readily available and much cheaper, it can be used instead of MRI to determine uterine volume.

INTRODUCTION

Hysterectomy is one of the most frequently performed gynecological operations. In the Netherlands around 15.000 hysterectomies are being performed each year [1]. The most common reason for hysterectomy are benign conditions, such as uterine fibroids [2]. Whenever a hysterectomy is scheduled, Uterine Volume (UV) is important in determining the surgical approach, i.e. transvaginally, laparoscopically (assisted), or transabdominally. Vaginal hysterectomies are considered superior in terms of costs and complications [3-6]. Several uterine volumes have been suggested as the maximal size for the vaginal route (with or without morcellation): 280 grams [7], 400 grams [8], and even up to 1300 grams [9]. Uteri larger than 280 grams are generally advised to be removed abdominally [10]. Furthermore, higher UV is associated with a higher risk of surgical complications [11].

In daily clinical practice, the volume of a fibroid uterus before hysterectomy usually is assessed by bimanual examination and confirmed by ultrasonography. Since uterine artery embolization (UAE) has become a popular treatment modality for the fibroid uterus, Magnetic Resonance Imaging (MRI) is increasingly being applied for the evaluation of uterine volume. Several articles have focused on the measurement of uterine size [12-14]. Only few studies, however, have compared uterine volume measured at bimanual examination and ultrasound to true uterine volume as obtained during histopathological examination, this being the gold standard [15;16].

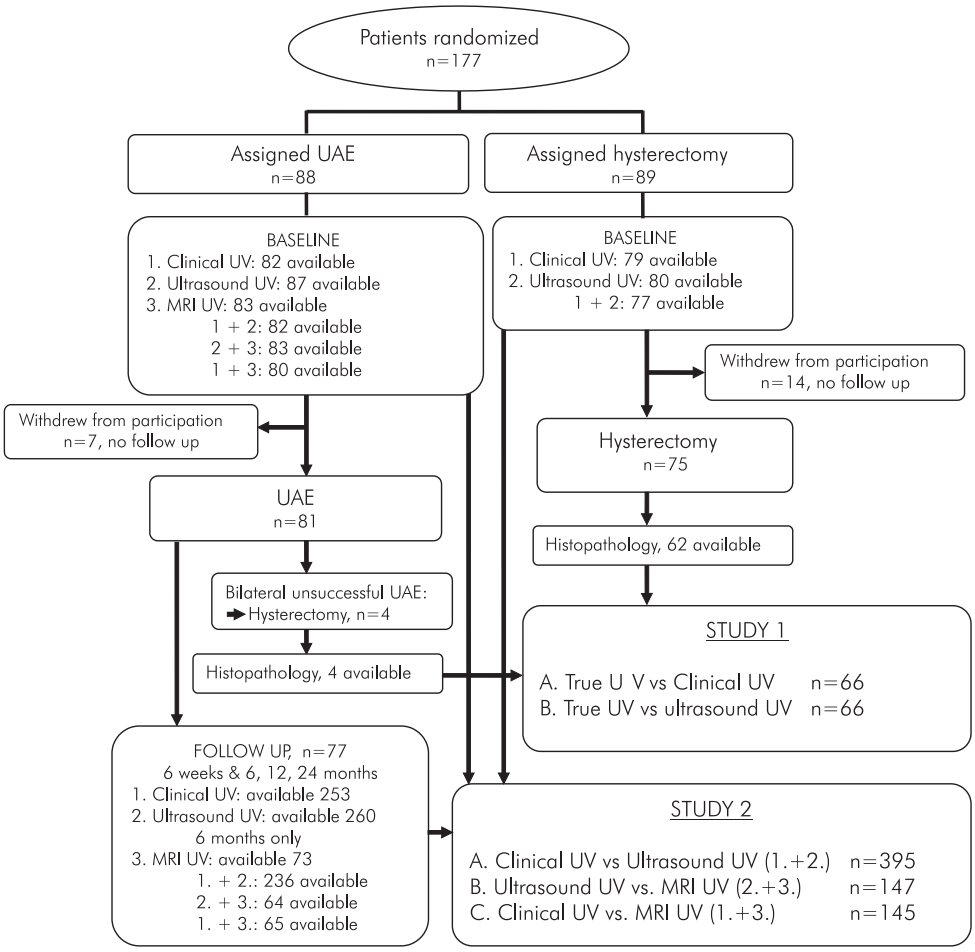
The aim of this study was to compare pre-operative uterine volumes estimated by bimanual examination and ultrasonography with actual uterine volumes obtained from histopathology reports of hysterectomized uteri, thus assessing the accuracy of these clinical methods in estimating uterine volume. Furthermore estimates from bimanual examination and ultrasonography were compared with MRI measurements.

METHODS

STUDY DESIGN

We used data collected alongside the prospective randomized multi-centre EMMY-trial in which hysterectomy and uterine artery embolization (UAE) for the treatment of symptomatic fibroids were compared [17]. Eligible patients were pre-menopausal, had symptomatic uterine fibroids and had no other treatment option than hysterectomy. Patients were randomly allocated (1:1) to hysterectomy or UAE by computerized randomization (Figure 1). Details of the study have been described elsewhere [17]. Figure 1 also describes the flow of patients and the available measurements for each diagnostic modality. At the pre-procedural visit

FIGURE 1. Flow chart



all (UAE and hysterectomy) patients underwent bimanual vaginal examination and a pelvic ultrasonography. Additionally, women randomized to UAE received a pelvic MRI. In the hysterectomy group, uterine volume was obtained after surgery. Four patients in the UAE group underwent a hysterectomy due to bilateral technical failure. In the UAE group where the uterus remained in situ, bimanual examination and ultrasound were repeated at 6 weeks and at 6, 12 and 24 months follow-up; the pelvic MRI was repeated only once, at 6 months after the intervention.

DETERMINING UTERINE VOLUME (UV)

In this manuscript uterine volume is expressed in grams, since the density of uterine tissue is the same as that of water. Thus 1 mL uterine volume equals 1 gram of uterine tissue [18].

TABLE 1. Conversion of uterine size as measured by bimanual examination (weeks) into uterine volume (Clinical UV) [9]

Uterine size (weeks)	Uterine volume (grams) mean (± SD)
6	113 (± 48)
8	141 (± 66)
10	172 (± 82)
12	233 (± 113)
14	321 (± 160)
16	465 (± 209)
18	747 (± 311)
20	1046 (± 464)
22	1246 (± 588)
24	1459 (± 479)
26	1730 (± 713)

Histopathological examination (gold standard)

The true uterine volume (referred to as 'True UV') obtained from the pathology reports was considered the gold standard. The removed uteri were weighed directly after surgery as part of the routine histopathological examination.

Bimanual examination

Bimanual examination was performed by a senior resident or gynecologist. The size of the uterus was expressed in weeks. If uterine size was expressed as a range, the mid value of the range was used as point estimate in the analysis. Uterine size (weeks) was then converted into uterine volume (grams) using the reference table for non-gravid uteri published by Harb et al. (Table 1) [15]. Uterine sizes larger than 26 weeks were not included in the analysis. Uterine volume yielded by bimanual examination is referred to as 'Clinical UV'.

Ultrasound and MRI

A transvaginal ultrasound was performed with 5–6.5 MHz transducers while in transabdominal ultrasonography a 3.5 MHz linear or sector transducer was used. The ultrasound was performed by a senior resident or a gynecologist. Three uterine dimensions (length, width and antero-posterior diameter) were obtained and recorded in cm. The uterine length (L) was the distance between the external cervical os to the dome of the fundus; the width (W) and antero-posterior (AP) diameter were taken perpendicular to the axis of the uterine length. MR imaging was performed using different brands of 1.0 T or 1.5 T MRI scanners all equipped with a phased array body coil. Sagittal T_1-weighed TSE images were performed as well as T_2-weighted images in sagittal, axial and coronal direction with slices orientation perpendicular and parallel to the long axis of the uterine cavity. Three dimensions (length, width and antero-posterior diameter) were measured similar to ultrasound. The dimensions were measured by

a senior resident or a radiologist. UV estimated by ultrasound ('Ultrasound UV') and MRI ('MRI UV') can be calculated using two formulas, which are based on the ellipsoid shape of the uterus: 'L × W × AP × 0.52 [15]' and '50 + (4/3 × π × L/2 × W/2 × AP/2) [16]'. Since these formulas proved to be equally predictive of uterine volume we have chosen the first equation [15].

COMPARISONS OF THE STUDY (FIGURE 1)

In Study I True UV was compared with Clinical UV (A) and Ultrasound UV (B).

The aim of Study II was to compare the accuracy of Clinical UV versus Ultrasound UV versus MRI findings. Three comparisons were made: A: Clinical UV versus Ultrasound UV; B. Ultrasound UV versus MRI UV; C. Clinical UV versus MRI UV.

STATISTICAL ANALYSIS

Analysis was done using SPSS statistical software (version 11.5.1).

The correlation between Clinical UV and Ultrasound vs. True UV as obtained from the pathology reports (Study I) was analyzed with two methods: Pearson's product moment correlation coefficient and the Intraclass Correlation Coefficient (ICC). Agreement between methods was described as mean difference (95%CI of the mean difference). Mann-Whitney-U tests were performed to evaluate whether uteri >280 grams (i.e. uterine volume above which abdominal surgery is recommended) rendered larger differences between the groups compared to uteri <280 grams.

The correlations between Clinical UV versus ultrasound UV versus MRI UV (Study II) were compared with Pearson's product moment correlation coefficient (Pearson) and the Intraclass Correlation Coefficient (ICC). ICC and Pearson were interpreted as follows: <0.20: poor; 0.20-0.40: fair; 0.41-0.60: moderate; 0.61-0.80: good; 0.81-1.00: excellent [19]. A p-value <0.05 (two sided) was considered statistically significant.

Agreement in Study II was expressed as the limits of agreement according to the Bland-Altman method [20]. For the Bland-Altman plots the limits of agreement were calculated as ± 2 SD of the mean difference in uterine volume. The limits of agreement between two methods indicate that about 95% of the observations/measurements are between the upper and lower limit, as indicated. The interpretation of the plots is as follows: when uterine volume is measured by two methods, producing two volumes, it is expected (with 95% confidence) that the estimated difference between the volumes is less than ± 2SD. When the limits are wide, i.e. ± 2SD of the mean difference is large, agreement between the two methods is poor. Similarly, small limits indicate substantial agreement between methods [20]. Large limits refer to clinically relevant differences: when standard deviation may lead to a clinically false

interpretation, e.g. choosing the vaginal route when the abdominal route would be more appropriate. Furthermore LOA were calculated for uteri smaller and larger than 280 grams (averaged between modalities as in Bland Altman plots).

To evaluate whether Body Mass Index (BMI, measured as weight (kg)/ length^2 (m)), parity and ethnicity had any impact on the discrepancies of estimated uterine volume between methods, univariate analysis of variance was performed with BMI (non-obese: BMI$\leq$ 25 versus obese: BMI>25), parity (nulliparity versus multiparity) and ethnicity (white versus non-white) as independent variables, and the difference in uterine volume between (i) Clinical UV versus True UV and (ii) Ultrasound UV versus True UV as dependent variables.

RESULTS

PATIENTS

Between March 2002 and February 2004, 177 patients were randomized in the EMMY study: 89 were allocated hysterectomy and 88 were allocated UAE (Figure 1).

For Study I, the comparison between Clinical UV, Ultrasound UV and True UV, we included 66 patients for whom the data on the pre-procedural bimanual examination, pelvic ultrasound of the uterus and uterine volume after hysterectomy were complete (Group 1).

For Study II, we included all available measurements at all time points (Figure 1). This resulted in 395 available measurements for comparison A (Clinical UV versus Ultrasound UV); 147 available measurements for comparison B (Ultrasound UV versus MRI UV) and 145 available measurements for comparison C (Clinical UV versus MRI UV). Data from all 177 patients were used in these comparisons (Group 2).

TABLE 2. Baseline characteristics

	Group 1 n=66	Group 2 n=177
Age (years)		
Mean (SD)	44.8 (4.2)	45.0 (4.5)
Ethnicity (n (%))		
Black	16 (24.2)	44 (24.8)
White	39 (59.1)	110 (62.1)
Other	11 (16.7)	23 (13.0)
Parity (n (%))		
≥ 1	48 (72.2)	127 (71.7)
0	18 (27.3)	50 (28.2)
BMI (kg/m^2)		
Mean (SD)	26.1 (4.8)	26.0 (4.9)

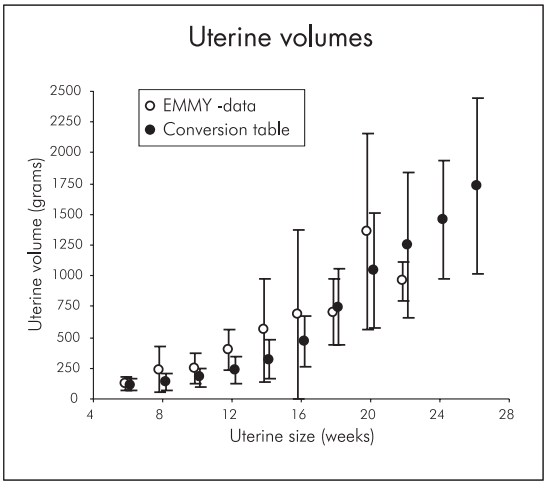


FIGURE 2. Bimanual uterine size and true uterine volume according to the conversion table and our study data

Table 2 presents the baseline characteristics for the patients used in both groups. Patients in both groups were on average 45 years old, were predominantly white (about 60%) and most had had children (about 72%). The mean BMI was 26 (SD=4.8).

STUDY I: CLINICAL UV AND ULTRASOUND UV VERSUS TRUE UV

Mean True UV was 581 grams (SD: 586; Range: 60-3040). Figure 2 shows the relationship between Clinical UV in weeks and True UV according to the pathological examination for the patients in our study compared to the reference data from the study by Harb et al [15]. Overall, our data were very similar to these reference data.

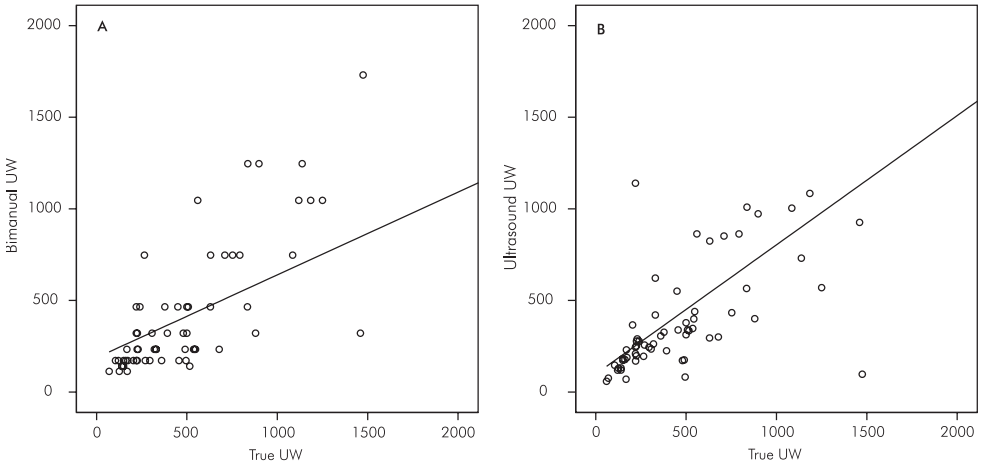
Table 3 summarizes Uterine Volumes as estimated bimanually, by ultrasound and at pathology. True UV was on average 117 grams higher than Clinical UV (95%CI: 17 to 217; p=0.02). True UV was 62 grams higher than Ultrasound UV, but this difference did not reach statistical significance (95%CI: -49 to 172; p=0.27).

TABLE 3. Outcomes of Study I and II

	Number (n)	Pearson correlation	ICC (95%CI)	Mean difference in grams (95%CI)	Limits of agreement in grams (±2SD)
Study I					
True UV – Clinical UV	63	0.63	0.58 (0.38-0.72)	117 (17 to 217)	NA
True UV – Ultrasound UV	65	0.65	0.64 (0.47-0.77)	62 (-49 to 172)	NA
Study II					
Clinical UV - Ultrasound UV	395	0.57	0.55 (0.48-0.62)	70 (36 to 103)	± 676
Ultrasound UV - MRI UV	147	0.78	0.75 (0.67-0.81)	16 (-42 to 74)	± 713
Clinical UV - MRI UV	145	0.72	0.67 (0.57-0.75)	20 (-42 to 83)	± 765

UV: uterine volume; ICC: intraclass correlation coefficient; CI: confidence interval; NA: not applicable; SD: standard deviation

FIGURE 3. The association of True UV with Clinical UV (A) and Ultrasound UV (B)



Agreement between Clinical UV and True UV was moderate to good (ICC=0.58; Pearson's correlation coefficient =0.63). Agreement between Ultrasound UV and True UV was good (ICC=0.64; Pearson's correlation coefficient =0.65).

Figure 3 displays the association between Clinical UV and True UV (panel A) and between Ultrasound UV and True UV (panel B), respectively.

Comparing volumes of uteri larger or smaller than 280 grams revealed a significant difference in the Clinical UV group, compared to True UV (True UV minus Clinical UV: <280gr.: mean difference: -48 gr. (SD 125); >280gr.: mean difference: +212 gr. (SD 464); p=0.0004). This indicates that Clinical UV underestimates large uteri and tends to overestimate small uteri. This was also the case with Ultrasound UV versus True UV (True UV minus Ultrasound UV: <280gr.: mean difference: -47 gr. (SD 188); >280gr: mean difference: +130 gr. (SD 539); p=0.001). Also Ultrasound UV underestimates large uteri and overestimates small uteri.

BMI was not associated with significant differences, neither for Clinical UV minus True UV (p=0.25) nor for Ultrasound UV minus True UV (p=0.23). We also investigated the effect of parity and ethnicity on the difference between True UV and Clinical UV and between True UV and Ultrasound UV respectively. There was neither significant effect of parity (True UV vs. Clinical UV: p=0.48; True UV vs. Ultrasound UV: p=0.52) nor of ethnicity (True UV vs. Clinical UV: p=0.81; True UV vs. Ultrasound UV: p=0.39) on these differences.

STUDY II: BIMANUAL EXAMINATION VERSUS ULTRASOUND VERSUS MRI

Table 3 also displays the correlation coefficients between Clinical UV, Ultrasound UV and MRI UV. Correlation was moderate between Clinical UV and Ultrasound UV, good between Ultrasound UV and MRI UV, and good between Clinical UV and MRI UV. Furthermore the

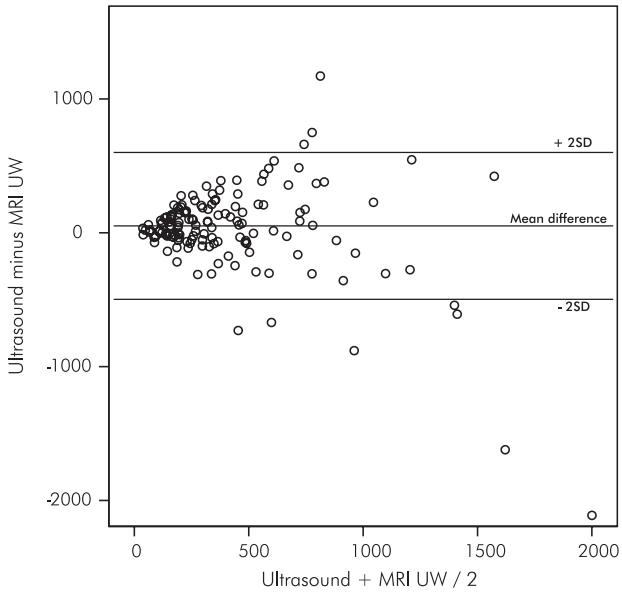


FIGURE 4. Bland-Altman plot with limits of agreement between MRI and Ultrasound UV

mean difference between various modalities is shown, together with the limits of agreement. Ultrasound UV was significantly higher than Clinical UV (mean difference: +70 grams; SD: 338; 95%CI: 36 to 103; p=0.0001). There was no significant difference neither between Ultrasound UV and MRI UV (p=0.59) nor between Clinical UV and MRI UV (p=0.52). For all combinations of various modalities, the limits of agreement ranged between 650-800 grams. Figure 4 shows the limits of agreement between Ultrasound UV and MRI UV. The LOA are wider for uterine volumes >280 grams compared to those of uteri <280 grams (Clinical UV and Ultrasound UV: ±683 versus ±110 grams; Ultrasound UV and MRI UV: ±1065 versus ±124 grams; Clinical UV and MRI UV: ±989 versus ±112 grams).

DISCUSSION

Our study demonstrated that Ultrasound UV correlates better with True UV than Clinical UV does. Furthermore, MRI and Ultrasound showed a good correlation. Clinical UV correlated well with MRI, but somewhat less with Ultrasound. No clinical factors were identified that could predict or explain the discrepancies between methods. Only for uteri >280 grams, a significantly larger dispersion was identified. Both bimanual and ultrasound examination tended to overestimate the volume of uteri <280 grams. This appears to be relevant in clinical practice: the indication for abdominal hysterectomy will be made more easily, thereby

not increasing the amount of conversions from vaginal to abdominal hysterectomy during surgery. On the other hand, abdominal hysterectomy might be performed, while vaginal hysterectomy would have been possible.

The moderate correlation between Ultrasound UV and Clinical UV was not confirmed by others: one study found a strong correlation between bimanual assessment and length of the uterus as measured by ultrasonography (correlation coefficient r=0.72) [12]. Another study found that ultrasonographic dimensions significantly correlated with the true dimensions of the removed uteri as described in histopathology reports [14]. None of these studies, however, compared bimanual and ultrasound volume with the actual uterine volume obtained at histopathological examination. Similar to our results, the study by Flickinger et al. found greater error in estimates of the actual uterine size by using bimanual examination than by ultrasonography, when compared with the actual uterine weight after hysterectomy [21]. In contrast, the study by Harb et al. found bimanual estimation to be the most accurate method [15]. However, these earlier studies were done retrospectively, unlike our study.

The comparisons between UV estimation methods may have been subject to specific measurement problems. First, bimanual examination yields a number referring to gestational uterine size which is then converted into grams according to uterine volumes rendered by a recent publication [15]. Since these data show substantial standard deviations, the uterine volumes may not be accurate. However, our data on average correlated fairly well with those of Harb et al. as demonstrated (Figure 2).

Similarly, ultrasound and MRI measurements were converted to grams using an equation which converts uterine size into uterine volume assuming that uteri are ellipsoid shaped, which often is not the case in reality. Multiple fibroids or irregular fibroids can easily transform the uterus into a different shape for which the formula apparently does not apply, producing underestimated or overestimated volumes, thereby increasing the inaccuracy between ultrasound and MRI UV versus other methods. The use of the same equation to estimate ultrasound UV and MRI UV might explain why agreement between these two is superior to comparisons with other methods.

Finally the measurement of True UV might be an underestimation of reality because uterine volume and thus weight might decrease during and soon after hysterectomy because of postoperative loss of blood, lymph and serum from the specimen and from evaporation at room temperature [22]. Although UV is important in determining the route of hysterectomy, other considerations are also important, e.g. uterine mobility and vaginal access, which is related to parity in terms of previous vaginal birth. Apart from uterine volume estimates, other diagnostic properties may be at stake during preoperative assessment of women planned

to undergo surgery, e.g. the presence of adenomyosis or uterine malignancies. Analysis of these diagnostic properties was not the scope of the present study.

In summary, our study shows that uterine volume estimated by ultrasound has the best correlation with true uterine volume. Ultrasound outperforms bimanually estimated uterine volumes and is about equally accurate compared to MRI. Since ultrasonography is easier accessible and much cheaper than MRI, it is the diagnostic method of choice for estimating uterine volume.

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UTERINE ARTERY EMBOLIZATION **VERSUS** HYSTERECTOMY FOR SYMPTOMATIC UTERINE FIBROIDS

IV

SUMMARY, GENERAL DISCUSSION AND CONCLUSION

15 SUMMARY, GENERAL DISCUSSION AND CONCLUSION

This thesis describes the results of the EMMY (EMbolization versus hysterectoMY) trial, a randomized controlled trial comparing uterine artery embolization (UAE) and hysterectomy in the treatment of symptomatic uterine fibroids. This chapter summarizes the findings from the EMMY trial, together with a general discussion that compares our results with the current literature. Furthermore, future research implications and final conclusions are discussed.

SUMMARY

Uterine fibroids are relatively common benign tumors in women of reproductive age: in the literature, the incidence has been reported to range from 5.5 to 77% [1;2], but most publications quote an incidence of 25%, referring to a review published in 1981 [3]. Not all uterine fibroids cause symptoms. The nature and severity of symptoms depend on the size of fibroids, their location in the uterus and their position in relation to other structures [4;5]. Symptoms include heavy menstrual bleeding (menorrhagia, i.e. either prolonged bleeding, severe bleeding or both), pain (during menstruation, during sexual activity or during activities of daily living) and pressure symptoms (urinary urgency, incontinence, and pressure sensations in the lower abdomen) [4;5]. Since fibroids rarely cause life-threatening symptoms and complaints usually resolve after menopause, a symptomatic treatment is restricted to women of reproductive age in the majority of cases [4;5]. Fibroid related complaints may well interfere with normal daily activities and sometimes cause social isolation, thus obviating the need for treatment.

Conservative therapeutic options include oral contraceptives, progestins, coagulation stimulants, GnRH-analogues and non-steroidal anti-inflammatory drugs [6;7]. Sometimes a hormone-releasing intrauterine system can offer symptomatic relief [8].

Hysteroscopic myomectomy is the first line surgical therapy for fibroids protruding into the uterine cavity by >50% [9]. If this is not the case, abdominal myomectomy may be indicated especially in women desiring future pregnancy [10].

Finally, when other therapies are not an option or provide unsatisfying results, a hysterectomy may offer the final solution for symptomatic relief.

In 1995 a new technique for the treatment of symptomatic uterine fibroids was introduced by Ravina et al.: uterine artery embolization (UAE) [11]. Small particles are injected into both uterine arteries by arterial catheterization, thus occluding uterine blood flow at the arteriolar level. This causes irreversible ischemic injury to the fibroids while avoiding permanent damage to the uterus. Deprived of the arterial blood supply, the fibroids will shrink and symptoms will subside. UAE was presented as a promising technique that might be able to replace hysterectomy altogether, for those women bound to undergo hysterectomy. No randomized

controlled trials were available however, to support these claims. For this reason the EMMY (EMbolization versus hysterectoMY) trial was designed in 2001 to compare two therapeutic strategies for the treatment of symptomatic uterine fibroids:

- UAE, a minimally invasive technique which conserves the uterus with the inherent risk of recurrent symptoms.
- Hysterectomy, a classical operative procedure where -by definition- the uterus is removed and which provides certainty of symptomatic relief.

TRIAL CHARACTERISTICS

The EMMY (EMbolization versus hysterectoMY) trial is a multi-center randomized controlled trial. A total of 349 eligible patients were asked to participate in 34 Dutch hospitals. Randomization was performed using a computer-based minimization scheme ('balancing procedure'), stratified for study center. Patients were followed up for 24 months. Data were analyzed according to the intention to treat principle.

Endpoints of the study

The EMMY trial was set up as a non-inferiority trial: the assumption that UAE would be clinically non-inferior to hysterectomy if clinical failures (defined as the need for a secondary hysterectomy within two years after UAE) occurred in < 25% of patients. This arbitrary 25% cut-off level was based on the design of other trials which compared minimally invasive procedures (i.e. endometrial ablation) to hysterectomy in providing symptomatic relief of menorrhagia [12-15].

Secondary endpoints included:

- Major and minor complication rates
- Duration of hospital stay
- Time to recovery
- Change in health related quality of life
- Effect on pain and pressure symptoms
- Impact on ovarian reserve
- Cost-effectiveness
- Patient's treatment preferences

In the UAE group the following additional parameters were investigated:

- Fibroid and uterine volume reduction
- Technical characteristics of UAE

Furthermore, various diagnostic techniques - i.e. bimanual examination, ultrasound and Magnetic Resonance Imaging (MRI)- used in this trial were analyzed in terms of validity and reproducibility.

Patients

Women were included when (1) uterine fibroids were present; (2) they were premenopausal; (3) menorrhagia was the major complaint; (4) treatment options other than hysterectomy were impossible or provided unsatisfactory results. Women were excluded if: 1) preservation of the uterus was warranted for future pregnancy, 2) renal failure (kreatinine > 150 mmol/L), active pelvic infection or clotting disorders were clinically established, 3) they were allergic to contrast material, 4) uterine malignancy was suspected, 5) submucosal fibroids with 50% of their diameter within the uterine cavity or pedunculated serosal fibroids were present.

Interventions

UAE was performed by interventional radiologists. The treatment took place under local anesthesia. A percutaneous catheter was introduced into the femoral artery using either a unilateral or bilateral technique and manipulated under fluoroscopic guidance into the uterine arteries. When the catheters were in place the embolization was carried out using polyvinyl alcohol (PVA) particles until flow in the fibroids subsided.

The hysterectomy was performed by a gynecologist, who decided on the type of hysterectomy and the route of access. Most hysterectomies were performed abdominally as is to be expected in enlarged fibroid uteri.

Study profile (chapter 2-11)

Patients were evaluated by a gynecologist at the outpatient clinic at baseline and at 6 weeks and 6, 12 and 24 months follow up. If applicable, the following investigations were performed at every visit: a case history, blood tests and ultrasound examination. Only in the UAE group an MRI scan was performed at baseline and at 6 months follow up. Self-reported questionnaires were administered by mail at baseline, 6 weeks and 6, 12, 18 and 24 months.

OUTCOMES OF THE STUDY

Patients (chapter 2)

28 hospitals recruited 177 out of 349 eligible patients for the trial from March 2002 until February 2004. The remaining 172 patients did not participate, mostly because of a strong treatment preference for hysterectomy (58%). Patients were randomized to UAE (n=88) or hysterectomy (n=89). The average age of participating patients was 44.6 years

(UAE) and 45.4 years (hysterectomy). Participants were predominantly Caucasians (UAE: 61.4%; hysterectomy: 64.0%). Most patients (85.3%) had already received one or more treatments for symptomatic uterine fibroids before study enrolment. Patients suffered from menorrhagia for a median of 24 months. The median number of fibroids was two in both groups. Mean uterine volume was 321 cm^3 in the UAE group compared to 313 cm^3 in the hysterectomy group. Eventually 81 patients assigned to the UAE group underwent the procedure compared to 75 patients in the hysterectomy group. The remainder of patients withdrew from the study.

PART I: SHORT TERM RESULTS

Failures and complications until 6 weeks after discharge (chapters 2 and 5)

No technical failures occurred in the hysterectomy group. Bilateral UAE failure occurred in 4 patients (4.9%). These patients underwent a hysterectomy, but were followed up in the UAE group according to the intention to treat principle. Major complications were relatively rare: 4.9% (UAE) compared to 2.7% (hysterectomy) of cases (p=0.68). The major complications in the UAE group were: a pulmonary embolism (n=1), pneumonia in a patient with a history of recurrent pneumonia due to asthmatic disease (n=1), surgical intervention because of an incomplete fibroid expulsion (n=1) and septicemia (n=1). In the hysterectomy group two major complications occurred: a pulmonary embolism (n=1) and a vesicovaginal fistula (n=1). The minor complication rate before discharge did not differ significantly between UAE and hysterectomy (22% vs. 31%; p=0.23), while the minor complication rate from discharge until 6 weeks thereafter proved to be significantly higher in the UAE group (58% vs. 40%; p=0.02). Based on our results UAE is a safe procedure with comparable complication rates to hysterectomy.

Technical characteristics of UAE (chapter 3)

The inability to embolize a uterine artery occurred in 14/81 (17.3%) of cases, of which 4/81 bilateral and 10/81 unilateral failures. The true technical failure rate, due to technical difficulties, according to the Society of Interventional Radiology (SIR) guidelines was 5.3%. The remaining failures occurred mainly because of absent uterine arteries or a non-dominant flow to the fibroids and were therefore unavoidable. The risk of technical failure was found to be significantly associated with a single fibroid and/or a small uterine volume (<500cc). The use of larger amounts of embolization material was associated with the onset of post-intervention fever, major complications and high pain scores.

Hospital stay and readmissions in the first 6 weeks (chapter 4)

UAE patients were admitted to the hospital for an average of 2.5 days (including re-admission time) compared to 5.1 days for hysterectomy patients ($p<0.001$). UAE patients were more often readmitted (11.1% vs. 0%; RR: not applicable; $p=0.003$). 7 out of 9 readmissions (77.8%) occurred within the first week after discharge. Patients were mostly readmitted for pain (22%), fever (22%) or both (44%). One readmission (11%) was because of a fibroid expulsion.
Thus, hospitalization is shorter after UAE than after hysterectomy.

Pain (chapter 4)

Post-procedural pain during hospitalization as measured by the Numerical Rating Scale (NRS) pain scores was significantly higher in the hysterectomy group during the first 24 hours ($p=0.015$). The time for patients to become pain-free after discharge did not differ between the groups (log rank test: $p=0.13$). After discharge, the time for 50% of patients to become free from pain was 7 days for UAE patients compared to 10 days for hysterectomy patients.

Recovery (chapter 4)

UAE patients resumed all of the following activities significantly earlier than hysterectomy patients: work (mean: 28 versus 63 days); doing household activities (mean: 12 versus 29 days); doing groceries (mean: 14 versus 35 days); activities with their children (mean: 17 versus 30 days) (all $p<0.001$).

PART II: LONG TERM RESULTS

UAE clinical failures (chapter 6)

Two years after UAE treatment 19/81 (23.5%) patients had undergone a hysterectomy. Of these, 4/19 (21%) underwent a hysterectomy because of immediate technical failure of the embolization procedure, while 15/77 (19.5%) had a secondary hysterectomy because of clinical failure after a technically successful UAE procedure. The secondary hysterectomies were distributed evenly over the two years follow up period.
This chapter concluded that an intended UAE resulted in 23.5% secondary hysterectomies, i.e. below the preset cut-off level of 25%, implying that indeed UAE was clinically non-inferior to hysterectomy. After a successful UAE procedure the clinical failure rate was 80.5%.

Re-interventions (chapter 6)

In the UAE group 4 additional procedures were carried out apart from secondary hysterectomies: 2 hysteroscopic procedures for removal of necrotic fibroid tissue, 1 incisional hernia repair (after secondary hysterectomy), and 1 diagnostic hysteroscopy for

postmenopausal bleeding. In the hysterectomy group 6 patients (8.0%) underwent additional re-interventions: 1 incisional hernia repair, 1 Latzko-repair of a vesico-vaginal fistula and 3 laparoscopies and 1 laparotomy for persistent abdominal pain after the primary treatment. These four patients continued to have persistent abdominal pain at 24 months follow-up.

Menstrual bleeding (chapter 6)

After 2 years 50/81 (61.7%) UAE patients were completely symptom free (including those patients who underwent a secondary hysterectomy), while 28/81 (34.6%) patients experienced slight or moderate improvement of complaints compared to baseline. The remaining 3/81 (3.7%) patients described their menorrhagia as being unchanged compared to baseline. As was to be expected, all hysterectomy patients were symptom free during the entire follow up period. At 24 months the hemoglobin levels had increased significantly compared to baseline in both groups (at 24 months: UAE: +0.85 mmol/l; hysterectomy: +1.26 mmol/l). Increase of hemoglobin levels was significantly higher for hysterectomy patients ($p=0.037$).

Pain and bulk symptoms (chapter 6)

Pain complaints improved in a large number of patients compared to baseline: 84.9% (UAE) and 78.0% (hysterectomy). Also bulk-related complaints improved for the majority of patients: 66.2% and 69.2% for UAE and hysterectomy patients respectively. No differences in improvement of pain and bulk complaints were observed between both treatment arms. Uterine and dominant fibroid volumes in UAE patients were reduced by 48.2% and 60.5% at 24 months follow up.

Impact on ovarian reserve (chapter 7)

Impact of both treatments on ovarian reserve was tested by means of both hormonal parameters (i.e. Follicle Stimulating Hormone (FSH), Anti-Müllerian Hormone (AMH)) and by clinical parameters (validated questionnaires about menopausal symptoms). AMH reflects the number of oocytes in the ovaries.

FSH increased significantly compared to baseline in both groups after 24 months follow up (UAE: +12.1 IU/l; hysterectomy: +16.3 IU/l). No differences between the groups were found ($p=0.32$). At 24 months the number of patients with FSH levels >40 IU/L (the definition of menopause) was 14/80 (17.5%) in the UAE group and 17/73 (23.3%) in the hysterectomy group ($p=0.37$). At 24 months, AMH levels in the UAE group were significantly decreased compared to the expected AMH decrease ascribed to ageing ('natural course'). This was not the case in hysterectomy patients. No differences were observed between the groups.

Both treatments seem to have an adverse impact on ovarian function. UAE might have a more severe impact on ovarian reserve than hysterectomy.

Health-related quality of life (chapter 8)

Health related quality of life (HRQOL) was assessed by validated questionnaires. General health was measured by the Medical Outcomes Study Short Form-36 (SF-36). SF-36 yielded two scores: the Mental Component Summary (MCS) and the Physical Component Summary (PCS). Both MCS and PCS improved significantly in both treatments. No differences were observed between the two treatment groups. At 24 months the MCS in the UAE group improved an average of 5.8 points versus 7.3 in the hysterectomy group (mean difference: 1.5; p=0.50). For the PCS this was +9.4 and +9.3 respectively (mean difference: -0.1; p=0.95). Average HRQOL improved until 6 months after treatment and stabilized thereafter during the entire follow up period in both treatment arms. Other validated questionnaires (HUI-3 and EuroQol-5D) showed similar results. The same improvement was observed for urinary symptoms as measured by the Urinary Distress Inventory (UDI). The Defecation Distress Inventory (DDI), which investigates defecation function, displayed improvement only in the UAE group at 24 months compared to baseline. In the hysterectomy group no significant change from baseline was observed. General physical health (PCS) was better in patients who did not require a secondary hysterectomy compared to those patients who did (p=0.021).
In general, both treatments improve HRQOL equally.

Satisfaction (chapter 8)

Satisfaction was measured using a 7-point Likert scale at all follow up moments. At 24 months, most patients in both groups were at least moderately satisfied (UAE 92.5% versus hysterectomy 90.4%). At 24 months hysterectomy patients were overall significantly more satisfied than UAE patients (p=0.02).

Sexual function and body image (chapter 9)

The impact of both treatments on sexual functioning was investigated using the validated Sexual Activity Questionnaire (SAQ). Sexual functioning improved in both treatment groups, but a significant change from baseline was only observed after UAE for the dimensions 'discomfort' and 'habit'. At 24 months, no statistically significant differences were observed between the treatment arms. The overall quality of sexual life deteriorated in a minority of cases at all time points (at 24 months: UAE: 29.3% versus hysterectomy: 23.5%; p=0.32).

Also body image, as measured by the Body Image Scale (BIS), improved in both groups, but only significantly so in the UAE group at 24 months compared to baseline (p=0.009). No significant differences were observed between the groups.
Thus, both treatments improved sexuality and body image, but only significantly so in the UAE group.

Cost-effectiveness (chapter 10)

Given the absence of significant differences between the groups in HRQOL over time, a cost-minimization analysis was chosen as economic framework. The direct medical in-hospital costs (i.e. all costs generated during hospital stay and possible re-admissions during follow-up) were 20% lower in the UAE strategy: $6688 vs. $8313 (mean difference: $1624/ €1212). Direct medical out-of-hospital and direct non-medical costs were low in both groups (mean cost difference: $156/ €116 in favor of hysterectomy). The indirect costs (i.e. costs related to absence from work) differed significantly between the treatment strategies in favor of UAE (mean difference: $5453/ €4069). The costs of absence from work accounted for 79% of the difference in total costs. At two years follow-up the mean total costs per patient in the UAE group were 37% lower than in the hysterectomy group ($11626 vs. $18563; mean difference $6936/ €5176).

According to the sensitivity analysis, overall cost differences were relatively insensitive to variations in four important cost parameters, implying that the cost difference in favor of UAE was robust.
From an economic perspective, uterine artery embolization is the superior treatment strategy for patients with symptomatic uterine fibroids.

Treatment burden and patients' treatment preferences (chapter 11)

Patients' anticipated burden at baseline for hysterectomy was higher than for UAE, especially with regard to the hospital admission, post-procedural pain and discomfort. However, after the allocated treatment had been performed the actually experienced burden was lower than expected in both groups, especially in the hysterectomy group. When the overall success rates of UAE were varied from 60% to 98% success, the group that preferred UAE did not change substantially, indicating that women opting for UAE were willing to accept this treatment even at lower success rates (i.e. 60%).
Before randomization women in both treatment groups expressed a higher preference for UAE (UAE: 75.0%; hysterectomy: 63.4%). After treatment, however, the majority of patients preferred the treatment they had actually received.

At 24 months, there was no effect of having undergone the preferred treatment or not on quality of life (difference in SF-36 PCS and SF-36 MCS change scores; p=0.51 and p=0.71 respectively) or satisfaction ratings (p=0.34).
Since the primary clinical endpoint and the HRQOL outcomes after UAE and hysterectomy did not differ significantly, patients' treatment preference should be allowed to play a decisive role in the choice of treatment.

PART III: VALIDATION AND RELIABILITY

Impact of randomization on outcome (chapter 12)

In this chapter we compared the women who participated in our trial (the 'randomized group', n=177) with the group of eligible women who refused to participate in the trial and followed their own treatment preference (the 'preference group', n=172). The randomized and the preference group were compared in terms of quality of life (as measured by the SF-36 questionnaire) at baseline and 12 month follow-up. At baseline, the preference group reported significantly better mental health than the randomized group (SF-36 MCS score: 46.1 vs. 41.1, p<0.0001). There was no difference in physical health at baseline (SF-36 PCS: 43.7 vs. 42.9; p=0.49). At 12 months follow-up the difference in mental health between the groups was not significantly different (mean difference SF-36 MCS: -2.62; p=0.15), while the improvement in physical health was significantly higher in randomized women (mean difference SF-36 PCS: 5.97; p=0.001).
Apparently, patients with worse mental health were more inclined to participate in the EMMY trial than patients with better mental health. Furthermore, participants in our trial experienced more physical health improvement than those women following their own preference.

Scoring of MRI images (chapter 13)

The digital MRI images rendered in the UAE–arm of the EMMY study were used to evaluate inter- and intra-observer variability for fibroid specific parameters. The images were assessed on two separate occasions by two blinded observers. Inter-observer agreement of uterine volumes, dominant fibroid volumes, number of fibroids and location of the dominant fibroid was very good (ICC=0.99, ICC=0.98, ICC=0.88, κ=0.82). Intra-observer variability had similar favorable results.
This study demonstrated that MR imaging criteria used for the selection of suitable UAE patients showed a good inter- and intra-observer reproducibility, thereby confirming that commonly used MR imaging prior to UAE is reliable.

Comparing vaginal examination with imaging modalities (chapter 14)

In this sub-study we compared different strategies that were used in the EMMY-trial to determine Uterine Volume (UV): bimanual examination ('Clinical UV') and ultrasound estimation ('Ultrasound UV') were compared to histopathology evaluation ('True UV'). Furthermore MRI estimation ('MRI UV') was compared with Ultrasound UV and Clinical UV. Correlation between Ultrasound UV and True UV was good (ICC=0.64). Correlation between True UV and Clinical UV was moderate (ICC=0.58). Agreement between MRI and Ultrasound UV was good (ICC=0.75), the same accounted for MRI UV and Clinical UV (ICC =0.67). Agreement between Clinical UV and Ultrasound UV was moderate (ICC=0.55). Thus ultrasound estimated uterine volume better than bimanual examination. Ultrasound was comparable to MRI and can therefore replace MRI for volume measurement.

GENERAL DISCUSSION

When this trial was designed only small uncontrolled case series were available which showed substantial improvement of menorrhagia after uterine artery embolization (UAE) [11;16-21]. According to these uncontrolled series, clinical effectiveness, defined as improvement in menorrhagia, averaged 85%. These promising results justified a randomized controlled trial to evaluate the true effectiveness of this new technique in comparison to established therapies such as hysterectomy.

While we conducted our trial, several larger cohort studies (>100 patients) were published reporting menorrhagia improvement in 83%-88% of women [22-25]. These high success rates were not confirmed by the first semi-randomized trial, which included 57 patients, 40 of whom underwent UAE and 17 of whom underwent a hysterectomy. This study reported a lower success rate of 79% [26]. Although this trial has been classified as a moderate quality RCT [27], it might however imply that UAE results depend on the selection of patients, which were all eligible for hysterectomy in this trial. In the United States a voluntary registry has recorded the results of 1797 UAE procedures [28]. Registries are known to provide low evidence (level 2c), as reflected by the insufflated clinical success rate of 97.1%, which is probably a gross overestimation of reality due to selection bias and inclusion of patients with less severe symptoms.

Uterine Artery Embolization: randomized evidence

After the publication of the initial results of our trial, the results of another randomized controlled trial evaluating UAE were published (the 'REST trial') [29]. In contrast to the EMMY

trial this study randomized patients to receive UAE (n=106) or the 'best surgical option' (i.e. hysterectomy (n=43) or myomectomy (n=8)) in a 2:1 fashion. For most outcomes the REST trial reported a follow up of 12 months, while we used a follow-up of 24 months. The results of both randomized trials are summarized in Table 1. To enable a comparison between both studies, we adapted our results to those of the REST trial: e.g. when the EMMY-trial results were presented as "mean" while the REST trial presented "medians", we changed our data accordingly. This explains any differences between Table 1 and results reported elsewhere in this thesis.

Many results are comparable. Clinical results like length of hospital stay, time to return to work, clinical failures rates (both around 20%), SF-36 scores and EQ-5 scores are very similar. There are however some differences. Baseline uterine volume was higher in the REST trial. Total direct medical in-hospital costs were calculated differently, explaining the

TABLE 1. Outcomes from the EMMY trial and the REST trial

	UAE		Hysterectomy*[1]	
	EMMY	REST	EMMY	REST
Baseline characteristics				
Number of patients	88	106	89	51
Age (mean in years)	44.6	43.6	45.4	43.3
Uterine volume (mean in cm3)	472	579	481	701
Menorrhagia as main symptom (%)	100	55	100	58
SF-36 MCS (mean, range: 0-100)	42	40	41	40
SF-36 PCS (mean, range: 0-100)	44	46	44	44
EQ-5 (mean, range: 0-100)	70	**70**	68	**63**
Procedural results				
Underwent assigned treatment (n)	81/88 (92%)	101/106 (95%)	75/89 (84%)	48/51 (94%)
Technical failure (n)	4/81 (5%)	3/101 (3%)	0/75 (0%)	1/48 (2%)
Short term results				
24 hr pain score (mean, range: 0-10)	3.1	**3.0**	3.9	**4.6**
Hospital stay (mean in days)	**2**	**1**	**5**	**5**
Return to work (median in days)	**21**	**20**	**56**	**62**
Long term results				
Clinical failures (n)	15/77 (19.5%)	18/98 (18.4%)	0/75	0/48
SF-36 MCS (mean at 12 months)	48	48	47	49
SF-36 PCS (mean at 12 months)	51	52	53	53
EQ-5 (mean at 12 months)	78	82	77	83
Costs (dollars) per patient *[2]	**6688**	**3109**	**8313**	**4811**

*[1] Or best surgical option in REST (myomectomy n=8); *[2] Costs only include direct medical in-hospital costs. Numbers presented in **bold** differed significantly between UAE and hysterectomy within a trial. No statistical differences could be calculated between the trials. SF-36: Medical Outcome Study Short Form-36; MCS: mental component summary; PCS: physical component summary. EQ-5: EuroQoL 5

difference in absolute costs for both treatments. However, the difference in mean direct medical in-hospital costs was very similar again (EMMY: $1625; REST: $1712).
As mentioned before, the follow-up period was also different: 1 year in the REST trial versus 2 years in the EMMY trial (the REST trial did also report beyond 12 months only in cases of clinical failure). Complication rates are difficult to compare since different classification systems were used: the REST trial used those of the Society of Interventional Radiology [30], which were only used in our trial for UAE patients (Chapter 4). Furthermore, their follow up for complications was 12 months, while complication rates in our UAE group were reported using the same classification until 6 weeks. Therefore complications cannot be compared properly.
From these randomized trials, including the previously mentioned small semi-randomized trial [26], it becomes apparent that the clinical success rate of UAE is approximately 80%. This is lower than the results reported in previously published case-series, probably because those studies had less rigorous data management in comparison to the RCTs and were prone to population bias where treated patients derived from a different clinical spectrum [27]. The indications to perform UAE are similar in all three RCTs, thereby yielding approximately the same results, underlining the importance of RCTs in evaluating new alternative treatments.

IMPLICATIONS

Whenever a hysterectomy is indicated for heavy menstrual bleeding due to uterine fibroids, UAE should be offered as an alternative treatment modality: patients' preferences for either treatment should be allowed to play a decisive role in the final treatment choice. The results presented in this thesis, together with those from the REST trial, provide convincing evidence to support this view. Constructive collaboration between gynecologists and radiologists is essential in optimizing further implementation of UAE, thus providing a solid platform for providing quality care and safety. To facilitate this process, guidelines for the Dutch Society of Obstetricians and Gynecologists (NVOG) and the Dutch Society of Radiologists (NVvR) will be needed, together with materials for patient education. It is our intention to assist in providing these requirements, which probably need to address the following subjects: 1) selection of patients; 2) procedural recommendations for performing UAE; 3) an advisory protocol for pre- and post procedural pain management; 4) a protocol for the nursing ward; 5) recommendations for patient follow up; 6) recommendations for counseling patients, including a patient information leaflet.

FUTURE RESEARCH

In this thesis the role of UAE as a valuable alternative to hysterectomy was established for those women not desiring future pregnancy. Obviously, these results cannot be extrapolated to patients who do have a desire for future pregnancy. A recent review revealed that complicated pregnancies and deliveries were more likely to occur after UAE compared to myomectomy. Pregnancies following uterine artery embolization were more at risk for preterm delivery (OR: 6.2, 95%CI: 1.4-27.7) and malpresentation (OR: 4.3, 95%CI:1.0-20.5) than pregnancies following laparoscopic myomectomy [31]. This review reported on uncontrolled case series due to the lack of randomized data. Therefore, randomized evidence is required to establish the exact role of UAE in women desiring pregnancy, especially in terms of obstetric outcomes. Designing an RCT for this group of patients is rather complicated: our results presented in chapter 10 imply possible ovarian damage from UAE, which may have serious consequences in women who wish to conceive. However, the average age of the women in our study was 45 years. The impact on ovarian reserve and function might be different in a younger population, and needs further evaluation. Theoretically, the ideal patients to include in such an RCT are those women with uterine fibroids related menorrhagia *and* a wish to preserve fertility. In these women, alternative options e.g. hormonal therapy are undesirable because of interference with fertility, while menorrhagia must be serious enough to warrant treatment. The proper control group would be those patients undergoing abdominal myomectomy, which also aims to preserve the uterus. The number of eligible patients for such a future trial, however, would probably be small and it would take quite a long time to reach sufficient power. An (international) multi-centre collaboration would be required to reach this objective.

Further research may also be valuable in optimizing the UAE procedure itself, thereby possibly increasing technical and clinical success rates. Firstly, micro-catheters are being used more frequently at present, thereby reducing arterial spasm which might improve technical- and clinical outcome [32]. Furthermore, the use of pre-procedural MRA imaging has been described, which gives information on the vascular anatomy before the actual UAE is undertaken. This might further reduce technical failure rates by improved patient selection [33]. Also, it has been opted to perform a post-procedural MRI shortly after UAE to establish the remaining vascularization [34]; in case of persistent flow to the fibroid re-embolization might be useful during the same hospital admission. Re-embolization procedures after clinical failure have also been performed with good results in a small uncontrolled series [35]. Future research has to elucidate the effect of repeat UAE and all other technical improvement measures on technical and clinical failure rates.

Unfortunately in our multiple regression analysis we found no baseline characteristics to predict clinical UAE success. Possibly in a larger group of UAE-patients predictors of UAE failure (or success) can be found, thereby improving patient selection and clinical success rates.
Theoretically, fibroids and menstrual bleeding symptoms can recur until menopause. Therefore it is our intention to continue the follow up of all our patients until menopause. This spring (2007), five years have passed since the first patient entered the EMMY trial. Within the next period of time we will analyze and publish our five years results. We aim to continue the follow up of our cohort of patients until menopause.

CONCLUSION

The EMMY trial investigated the value of uterine artery embolization (UAE) in comparison to hysterectomy in the treatment of symptomatic uterine fibroids.
We demonstrated that UAE offers a valuable alternative to hysterectomy. UAE was clinically non-inferior to hysterectomy (failure rate $<25\%$), and was equivalent to hysterectomy in terms of HRQOL, major complication rates and impact on ovarian function. UAE was superior in terms of hospital stay, resumption of daily activities and costs. Hysterectomy was superior in terms of minor complication rates, hemoglobin levels and patients' satisfaction. Since many important clinical outcomes showed no differences between both treatment modalities, other parameters emerging from this study, such as patients' preferences and costs, may further guide clinical decisions.

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16 SAMENVATTING, ALGEMENE DISCUSSIE EN CONCLUSIE

Dit proefschrift beschrijft de resultaten van de EMMY studie, een vergelijkend onderzoek tussen embolisatie en baarmoederverwijdering als behandeling van vrouwen met ernstige klachten ten gevolge van myomen. EMMY is een samentrekking van de Engelse termen voor deze behandelingen: EMbolization en hysterectoMY.
Onze resultaten worden tegen het licht gehouden van de wetenschappelijke literatuur over embolisatie van de baarmoeder. Voorts worden de conclusies en implicaties van het onderzoek besproken, en doen wij aanbevelingen voor toekomstig onderzoek.

SAMENVATTING

Myomen (ook wel 'vleesbomen' genoemd) zijn goedaardige gezwellen in de baarmoeder. Myomen komen veel voor: ongeveer 25% van de vrouwen in de vruchtbare levensfase krijgen een of meerdere myomen [1], hoewel de schattingen over het voorkomen van myomen erg wisselen (5.5 tot 77%) [2;3]. Myomen veroorzaken lang niet altijd klachten. De aard en de ernst van de klachten hangt af van de grootte van de myomen, hun positie in de baarmoeder en ten opzichte van andere organen zoals de blaas en de darmen [4;5]. De volgende symptomen kunnen door myomen ontstaan [4;5]: 1) menorrhagie klachten (overmatige en/of langdurige menstruaties), 2) pijn in de onderbuik (tijdens de menstruatie of bij dagelijkse activiteiten), en 3) klachten veroorzaakt door druk van de door myomen vergrote baarmoeder op de omliggende structuren, zoals loze aandrang, incontinentie, obstipatie of een opgeblazen gevoel.
De klachten die myomen veroorzaken zijn zelden levensbedreigend en meestal volstaat het om eventuele klachten te behandelen tot aan de overgang, aangezien myomen hierna kleiner worden en meestal geen klachten meer geven [4;5]. Hoewel de klachten niet levensbedreigend zijn, kunnen ze wel vervelende gevolgen voor het dagelijks leven hebben. Sommige patiënten raken in een sociaal isolement doordat de bloedingklachten zo hevig zijn dat ze de straat niet meer op durven.
Er zijn meerdere therapieën mogelijk voor de behandeling van myomen zoals hormonale behandelingen (de anti-conceptie pil, progestagen, GnRH-analogen) en niet-hormonale behandelingen (prostaglandinesynthetase remmers, stollingbevorderende medicijnen) [6;7]. Soms kan het Mirena spiraal uitkomst bieden [8].
Indien behandelingen met medicijnen niet helpen kan chirurgische behandeling overwogen worden. Wanneer de myomen voor meer dan 50% van de diameter uitpuilen in de baarmoederholte, is een hysteroscopische verwijdering van de myomen een effectieve behandeling [9]. Wanneer de myomen niet in de baarmoederholte uitpuilen, maar zich

in de wand bevinden of te groot zijn, wordt soms een operatie via de buik uitgevoerd waarbij de myomen chirurgisch uit de baarmoeder verwijderd worden (myomectomie) [10]. Deze behandeling wordt vooral toegepast bij vrouwen met kinderwens. Uiteindelijk, als conservatieve behandelingen onvoldoende helpen of niet verdragen worden, biedt een hysterectomie (baarmoederverwijdering) een definitieve oplossing voor het probleem.

In 1995 werd een nieuwe techniek geïntroduceerd voor de behandeling van symptomatische myomen door een Franse onderzoeksgroep onder leiding van dr. Ravina: embolisatie van de baarmoeder [11]. Bij deze techniek wordt onder lokale verdoving via liescatheterisatie kleine partikels in de arteriae uterinae (de slagaders die de baarmoeder van bloed voorzien) gespoten. Op deze manier wordt de bloedtoevoer naar de myomen geblokkeerd waardoor ze afsterven en kleiner worden, waardoor de klachten verminderen.

Embolisatie werd gepresenteerd als een veelbelovende techniek, die mogelijk een hysterectomie overbodig zou maken voor vrouwen met therapieresistente myomen van de baarmoeder. Toen de EMMY-studie werd opgezet (in 2001) bestond echter nog geen gerandomiseerde onderzoek waarin deze nieuwe techniek was vergeleken met hysterectomie. Juist dit gerandomiseerd onderzoek is noodzakelijk om aan te tonen dat embolisatie een alternatief voor hysterectomie is. De EMMY studie had tot doel in deze leemte te voorzien, door beide behandelingen met elkaar te vergelijken als behandeling van symptomatische myomen van de baarmoeder:

- Embolisatie, een relatief minder belastende ingreep waarbij de baarmoeder behouden blijft met het daaraan verbonden risico dat de klachten kunnen voortduren of terugkeren.
- Hysterectomie, een relatief ingrijpende operatie waarbij de baarmoeder verwijderd wordt, maar waarbij de symptomen die veroorzaakt worden door de myomen zeker zullen verdwijnen.

Hysterectomie is hier dus de gouden standaard waarmee de nieuwe techniek embolisatie vergeleken wordt.

STUDIE OPZET

De EMMY (EMbolization versus hysterectoMY) studie is een gerandomiseerd onderzoek waaraan meerdere ziekenhuizen hebben meegewerkt. In totaal werden 349 geschikte patiënten in 34 ziekenhuizen in Nederland gevraagd deel te nemen aan het onderzoek. Aan deelnemende patiënten werd door middel van randomisatie (loting) via een computerprogramma de behandeling toegewezen: embolisatie of hysterectomie. Hierbij werd gestratificeerd voor studiecentrum. Patiënten werden tot 24 maanden na de behandeling gevolgd. Bij de analyse van de gegevens werd het 'intention to treat' principe toegepast.

Vraagstellingen van de studie

Primaire vraagstelling:

De EMMY studie is opgezet als zogenaamde non-inferieuriteits studie: embolisatie zou klinisch niet-inferieur ten opzichte van hysterectomie zijn wanneer binnen twee jaar niet meer dan 25% van de embolisatie-patiënten alsnog een hysterectomie (zogenaamde secundaire hysterectomie) zou moeten ondergaan wegens onvoldoende klachtenverbetering.

Deze arbitraire grens van 25% is gebaseerd op de resultaten van soortgelijk onderzoek waarin hysterectomie werd vergeleken met andere baarmoedersparende ingrepen (zoals endometriumablatie) wegens hevige menstruele bloedingklachten [12-15].

Secundaire vraagstellingen:

De vergelijking tussen embolisatie en hysterectomie wat betreft:

- Optreden van ernstige en minder ernstige complicaties
- Duur van de ziekenhuis opname
- Herstel na ontslag uit het ziekenhuis
- Kwaliteit van leven
- Effect op pijn- en volumeklachten
- Invloed op de functie van de eierstokken
- Kosten-effectiviteit
- Behandelingsvoorkeur van de patiënt

In de embolisatie groep werden aanvullend de volgende parameters onderzocht:

- Volume reductie van baarmoeder en myomen
- Technische karakteristieken van embolisatie

Verder werden verschillende diagnostische technieken zoals vaginaal toucher, echo onderzoek en 'Magnetic Resonance Imaging' (MRI) onderzocht op validiteit en reproduceerbaarheid.

Patiënten

Vrouwen werd gevraagd deel te nemen aan het onderzoek wanneer ze aan de volgende criteria voldeden: 1) er bestonden myomen van de baarmoeder; 2) ze waren nog niet in de overgang; 3) hun voornaamste klacht was menorrhagie; 4) ze hadden geen andere behandelopties meer dan een hysterectomie; 5) ze wilden niet meer zwanger worden.

Verder moesten de volgende problemen afwezig: 6) nierfunctiestoornissen (kreatinine >150mmol/L), 7) infectie van het kleine bekken 8) stollingsstoornissen; 9) allergie voor contrastvloeistof; 10) verdenking op kanker van de baarmoeder; 11) gesteelde myomen die uitpuilden in de baarmoederholte of in de buikholte.

Behandelingen

De embolisatie werd uitgevoerd door een interventieradioloog. Onder locale verdoving werd via liescatheterisatie de arteria uterina beiderzijds opgezocht. Wanneer de catheters goed gepositioneerd waren werd de embolisatie uitgevoerd met behulp van PVA-partikels met een doorsnede van 355-500 μm. De partikels werden in de slagaders gespoten tot er in de myomen geen bloeddoorstroming meer zichtbaar was.

De hysterectomie werd door de behandelend gynaecoloog uitgevoerd. De behandelend gynaecoloog stelde ook het type hysterectomie en de toegangsweg (via de buik of de vagina of met laparoscopische technieken) vast. De meeste hysterectomieën werden echter uitgevoerd via de buik, aangezien de baarmoeder vaak fors vergroot was door de myomen.

Studie verloop (hoofdstuk 2-11)

De patiënten werden diverse malen op de polikliniek gezien door de behandelend gynaecoloog: voor de behandeling en 6 weken, 6, 12 en 24 maanden erna. Tijdens het poliklinisch bezoek werd een algemene anamnese afgenomen en werden de volgende onderzoeken uitgevoerd: lichamelijk onderzoek, laboratorium onderzoek en een echo onderzoek. Alleen in de embolisatie groep werd een MRI-scan verricht: voor de behandeling en 6 maanden erna.

Vragenlijsten werden per post verzonden, door de patiënten zelf ingevuld en teruggestuurd op de volgende momenten: voor de randomisatie, en 6 weken en 6, 12, 18 en 24 maanden na behandeling.

STUDIE UITKOMSTEN

Patiënten (hoofdstuk 2)

In de periode maart 2002 tot februari 2004 waren van de 349 geschikte patiënten er uiteindelijk 177 bereid tot deelname aan de studie. Het merendeel van de patiënten die deelname weigerden mee te doen (58%), wilden per se een hysterectomie ondergaan om er zeker van te zijn dat hun klachten zouden ophouden. De deelnemende patiënten werden gerandomiseerd tussen embolisatie (n=88) of hysterectomie (n=89). De gemiddelde leeftijd van de patiënten was 44.6 jaar (embolisatie) en 45.4 jaar (hysterectomie). De deelnemers waren overwegend blank (embolisatie: 61.4%; hysterectomie: 64.0%). De meeste patiënten (85.3%) hadden al voor aanvang van de studie een of meer behandelingen ondergaan vanwege myoom-gerelateerde klachten. Gemiddeld bestonden de menorrhagieklachten al 24 maanden. Het mediane aantal myomen was twee. Het gemiddelde volume van de baarmoeder was 321 cm^3 in de embolisatie groep vergeleken met 313 cm^3 in de hysterectomie groep. Uiteindelijk ondergingen 75 patiënten die geloot hadden voor

hysterectomie daadwerkelijk deze behandeling vergeleken met 81 patiënten in de embolisatie groep. De overige patiënten trokken zich uit het onderzoek terug.

DEEL I: KORTE TERMIJN RESULTATEN

Technische problemen en complicaties (hoofdstukken 2 en 5)

In de hysterectomie groep traden geen technische problemen op, terwijl het in 4/81 (4.9%) gevallen in de embolisatie groep niet lukte om beide arteriae uterinae te emboliseren. Deze 4 patiënten ondergingen een secundaire hysterectomie, maar werden geanalyseerd in de embolisatie groep (volgens het 'intention to treat' principe). Ernstige complicaties waren relatief zeldzaam: 4.9% na embolisatie versus 2.7% na hysterectomie, wat niet significant verschillend is ($p=0.68$). Het percentage kleine complicaties tijdens het verblijf in het ziekenhuis verschilde niet significant tussen de embolisatie- en de hysterectomie groep (respectievelijk 22% vs. 31%; $p=0.23$). Gedurende de eerste 6 weken na ontslag was het percentage kleine complicaties significant hoger in de embolisatie groep (58% vs. 40%; $p=0.02$).

Technische kenmerken van embolisatie (hoofdstuk 3)

Het bleek onmogelijk om de arteria uterina te emboliseren bij 14/81 (17.3%) van de patienten, waarvan 4/81 beiderzijds en 10/81 eenzijdig. De 'ware' technische onmogelijkheid ('true technical failure') om te emboliseren volgens de richtlijnen van de Society of Interventional Radiology (SIR) was 5.3%. De overige technische problemen werden veroorzaakt door onvermijdbare factoren, zoals een geheel afwezige arteria uterina of een niet-dominante bloedstroom naar de myomen. De onmogelijkheid om te emboliseren kwam significant vaker voor bij patiënten met een enkel myoom of een relatief kleine baarmoeder (<500cc). Er bestond een verband tussen de hoeveelheid gebruikt embolisatie materiaal en het optreden van koorts na de ingreep, ernstige complicaties en hoge pijnscores.

Ziekenhuisverblijf en heropnames in de eerste 6 weken (hoofdstuk 4)

Embolisatie patiënten waren gemiddeld 2.5 dagen opgenomen in het ziekenhuis (inclusief heropnames) vergeleken met 5.1 dagen bij hysterectomie patiënten ($p<0.001$). Embolisatie patiënten werden vaker heropgenomen (11.1% vs. 0%; $p=0.003$). 7 van de 9 heropnames (77.8%) in de embolisatie groep vonden in de eerste week na ontslag plaats, meestal wegens pijn (22%), koorts (22%) of beide (44%). Eén patient werd heropgenomen (11%) in verband met de expulsie van een myoom.

Pijn (hoofdstuk 4)

Pijn tijdens de ziekenhuisopname werd gemeten met de 'Numerical Rating Scale' (NRS) pijnscore. Pijnscores waren significant hoger in de hysterectomie groep gedurende de eerste 24 uur na de behandeling ($p=0.015$). De tijd tot het geheel verdwijnen van pijn na ontslag uit het ziekenhuis verschilde niet tussen de groepen (log rank test: $p=0.13$). De tijd totdat 50% van de patiënten pijnvrij was na ontslag uit het ziekenhuis was 7 dagen voor de embolisatie- en 10 dagen voor de hysterectomie groep.

Herstel (hoofdstuk 4)

Embolisatie patiënten konden elk van de volgende activiteiten significant het snelst hervatten: werk (gemiddeld: 28 versus 63 dagen); het huishouden doen (gemiddeld: 12 versus 29 dagen); boodschappen doen (gemiddeld: 14 versus 35 dagen); activiteiten ondernemen met de kinderen (gemiddeld: 17 versus 30 dagen) (allen $p<0.001$).

DEEL II: LANGE TERMIJN RESULTATEN

Het klinisch mislukken van embolisatie (hoofdstuk 6)

Twee jaar na de primaire behandeling hadden 19/81 (23.5%) embolisatie patiënten alsnog een hysterectomie ondergaan wegens onvoldoende verbetering of terugkeer van de menorrhagieklachten. Van deze patiënten ondergingen 4/19 (21%) een hysterectomie omdat de embolisatie beiderzijds mislukt was en 15/19 (79%) in verband met geen of onvoldoende verbetering van hun klachten. Dit betekent dat na een geslaagde embolisatie het aantal secundaire hysterectomieën 15/77 (19.5%) was. De secundaire hysterectomieën vonden gelijkmatig verspreid plaats over de 2 jaar follow-up periode. Concluderend vonden wij dat embolisatie bij 23.5% van de patiënten resulteerde in een secundaire hysterectomie. Dit percentage lag onder de vooraf vastgestelde bovengrens van 25%, zodat we kunnen stellen dat embolisatie non-inferieur is aan hysterectomie voor de behandeling van symptomatische myomen. Het succespercentage na een technisch geslaagde embolisatieprocedure bedroeg 80.5%.

Additionele behandelingen (hoofdstuk 6)

In de embolisatie groep werden, afgezien van de reeds genoemde secundaire hysterectomieën, nog 4 additionele procedures uitgevoerd: 2 hysteroscopische procedures waarbij afgestorven myoomresten werden verwijderd, 1 littekenbreukcorrectie (na secundaire hysterectomie) en 1 diagnostische hysteroscopie in verband met bloedverlies na de overgang. In de hysterectomie groep kregen 6 patiënten (8.0%) een additionele behandeling: 1 littekenbreukcorrectie, 1 Latzko-hersteloperatie voor een fistel tussen blaas en vagina en 3 laparoscopieën en 1

laparotomie in verband met persisterende buikpijnklachten na de initiële hysterectomie. Deze vier patiënten hadden nog steeds pijnklachten tijdens de laatste controle bij 24 maanden.

Menstrueel bloedverlies (hoofdstuk 6)

Na 2 jaar follow-up was 50/81 (61.7%) van de embolisatie patiënten geheel klachtenvrij (dit is inclusief de patiënten die een secundaire hysterectomie ondergingen), terwijl 28/81 (34.6%) patiënten een geringe tot redelijke verbetering van hun bloedingklachten had ten opzichte van de uitgangssituatie. De overige 3/81 (3.7%) van de patiënten beschreven hun klachten als onveranderd ten opzichte van het begin van de studie.

Na 24 maanden was het hemoglobine gehalte significant gestegen in beide groepen in vergelijking tot voor de ingreep (embolisatie: +0.85 mmol/l; hysterectomie: +1.26 mmol/l). Deze toename was significant hoger in de hysterectomie groep in vergelijking met de embolisatie groep (p=0.037).

Pijn en volumegerelateerde klachten (hoofdstuk 6)

Pijnklachten verbeterden bij 84.9% (embolisatie) en 78.0% (hysterectomie) van de patiënten ten opzichte van voor de behandeling. Ook volumegerelateerde klachten verbeterden bij de meerderheid van de patiënten (66.2% en 69.2% voor respectievelijk embolisatie en hysterectomie patiënten). Er bestond geen verschil tussen beide behandelingen wat betreft verbetering van pijn- en volume gerelateerde klachten. Bij embolisatie patiënten verminderden het volume van de gehele baarmoeder en van het grootste myoom met respectievelijk 48.2% and 60.5% na 24 maanden follow-up.

Invloed op de functie van de eierstokken (hoofdstuk 7)

Het effect van beide behandelingen op de functie van de eierstokken werd vastgesteld door bepaling van de volgende parameters: het Follikel Stimulerend Hormoon (FSH), het Anti-Müllerian Hormoon (AMH, een maat voor de hoeveelheid eicellen die nog in de eierstokken aanwezig zijn) alsmede door inventarisatie van overgangsklachten met behulp van gevalideerde vragenlijsten.

Na 24 maanden was het FSH significant gestegen in beide behandelingsgroepen ten opzichte van de uitgangssituatie voor behandeling: embolisatie: +12.1 IU/l; hysterectomie: +16.3 IU/l. Tussen beide groepen bestond echter geen verschil (p=0.32). Het aantal patiënten met een FSH gehalte >40 IU/L (als definitie van de overgang) bedroeg 24 maanden na embolisatie 14/80 (17.5%) en 17/73 (23.3%) na hysterectomie (p=0.37). In de embolisatie groep daalde het AMH sterker dan verwacht mocht worden op basis van natuurlijke

veroudering. Tussen beide groepen werd na 24 maanden echter geen significant verschil in AMH waarden gevonden.
Samenvattend lijken beide behandelingen schade toe te brengen aan de functie van de eierstokken, maar na embolisatie lijkt deze schade groter.

Kwaliteit van leven (hoofdstuk 8)

Kwaliteit van leven werd bepaald met behulp van gevalideerde vragenlijsten. Algemene kwaliteit van leven werd vastgesteld met de 'Medical Outcomes Study Short Form-36' (SF-36). De SF-36 berekent zowel een mentale (de MCS) als fysieke (de PCS) score. Zowel de MCS als de PCS verbeterde significant na beide behandelingen, terwijl er tussen de groepen geen verschillen werden gevonden. Na 24 maanden verbeterde de MCS score in de embolisatie groep gemiddeld met 5.8 punten versus 7.3 punten in de hysterectomie groep (gemiddeld verschil: 1.5; p=0.50). De PCS steeg met +9.3 punten in beide groepen (gemiddeld verschil: -0.1; p=0.95). De gemiddelde kwaliteit van leven verbeterde tot 6 maanden na de initiële ingreep, waarna deze stabiliseerde gedurende de verdere follow-up periode. Andere gevalideerde vragenlijsten over algemene kwaliteit van leven, zoals de 'HUI-3' en de 'EuroQol-5D' toonden vergelijkbare resultaten. Er werd ook een duidelijke verbetering van blaasklachten in beide groepen vastgesteld met behulp van de Urinary Distress Inventory (UDI) zonder verschillen tussen de groepen. De Defecation Distress Inventory (DDI), gericht op klachten met betrekking tot de ontlasting, liet alleen een verbetering zien in de embolisatie groep. In de embolisatie groep was de algemene fysieke gezondheid (SF-36 PCS) beter bij patiënten die geen secundaire hysterectomie ondergingen ten opzichte van degenen die bij wie dat wel nodig was (p=0.021).

Tevredenheid (hoofdstuk 8)

De algemene tevredenheid werd gemeten met behulp van een 7-punts 'Likert' schaal bij alle follow-up metingen. Na 24 maanden was de meerderheid van patiënten in beide groepen tenminste redelijk tevreden (embolisatie 92.5% versus hysterectomie 90.4%). Na 24 maanden waren hysterectomie patiënten significant meer tevreden dan de embolisatie patiënten (p=0.02).

Seksueel functioneren en lichaamsbeleving (hoofdstuk 9)

De invloed van beide behandelingen op het seksueel functioneren werd onderzocht met behulp van de gevalideerde vragenlijst: de Sexual Activity Questionnaire (SAQ). Het seksueel functioneren verbeterde alleen significant na embolisatie voor de dimensies 'ongemak' en 'gewoonte' ten opzichte van de uitgangssituatie. Na 24 maanden werd er echter geen verschil

in seksueel functioneren tussen de beide behandelingsgroepen aangetoond. De algehele kwaliteit van het seksuele functioneren verslechterde bij een minderheid van de vrouwen gedurende de gehele follow-up (na 24 maanden: embolisatie: 29.3% versus hysterectomie: 23.5%; p=0.32).
De lichaamsbeleving, gemeten met de gevalideerde Body Image Scale (BIS) verbeterde alleen significant in de embolisatie groep ten opzichte van de uitgangssituatie (p=0.009). Tussen beide behandelingsgroepen werden echter geen verschillen gevonden.

Kosten-effectiviteit (hoofdstuk 10)

Aangezien er geen significante verschillen werden gevonden tussen hysterectomie en embolisatie in kwaliteit van leven, besloten wij een kosten-minimisatie analyse uit te voeren. De direct medische kosten in het ziekenhuis (dit waren alle kosten gemaakt ter voorbereiding van de ingreep, van de ziekenhuisopname en ten gevolge van eventuele heropnames en re-interventies) waren 20% lager in de embolisatie groep: $6688 vs. $8313 (gemiddeld verschil: $1624/ €1212). Direct medische kosten buiten het ziekenhuis en directe niet-medische kosten waren laag in beide behandelingsgroepen (gemiddeld kosten verschil: $156/ €116 in het voordeel van de hysterectomie). De indirecte kosten, oftewel de kosten gerelateerd aan werkverzuim, verschilden significant in het voordeel van embolisatie (gemiddeld kosten verschil: $5453/ €4069). De kosten ten gevolge van het werkverzuim droegen voor 79% bij aan het verschil in totale kosten. Na 2 jaar follow-up waren de gemiddelde totale kosten per patiënt in de embolisatie groep 37% lager dan in de hysterectomie groep ($11626 vs. $18563; gemiddeld verschil: $6936/ €5176). Er werd tevens een sensitiviteitsanalyse uitgevoerd, waarin vier belangrijke kosten parameters sterk gevarieerd werden. Hieruit bleek dat alle verschillen in totale kosten tussen de behandelingsopties relatief ongevoelig waren voor variatie. Dit betekent dat het kostenverschil in het voordeel van embolisatie robuust is. Concluderend kon vastgesteld worden dat vanuit een economische perspectief embolisatie de superieure behandelingsoptie is voor patiënten met symptomatisch myomen.

Belasting van de behandelingen en behandelingsvoorkeur van de patiënt (hoofdstuk 11)

Voor de behandeling werd door de patiënten een inschatting gemaakt van de te verwachten belasting van beide behandelingen: de belasting van hysterectomie werd zwaarder ingeschat dan van de embolisatie procedure, vooral ten aanzien van de ziekenhuisopname, de postprocedurele pijn en het ongemak. Nadat zij daadwerkelijk behandeld waren echter, vonden patiënten de behandeling minder zwaar dan verwacht. Dit was vooral in de hysterectomie groep het geval.

Voordat de deelnemende patiënten geloot hadden tussen de twee behandelingen hadden meer vrouwen een voorkeur voor de embolisatie behandeling (embolisatie: 75% versus hysterectomie: 63%). Nadat de patiënten behandeld waren, prefereerde de meerderheid de behandeling die zij uiteindelijk hadden ondergaan.
Wanneer het fictieve succespercentage van de embolisatie procedure werd gevarieerd van 60% tot 98% succes, veranderde de voorkeur van de embolisatie groep voor embolisatie niet substantieel. Dit geeft aan dat patiënten, die kiezen voor een embolisatie, ook bereid waren lagere succespercentages te accepteren (bijvoorbeeld 60%).
Aangezien de primaire en secundaire klinische uitkomsten en de kwaliteit van leven niet significant verschilden tussen beide behandelingen, verdient de patiënten voorkeur een belangrijke rol bij de uiteindelijk behandelingskeuze.

DEEL III: VALIDATIE EN BETROUWBAARHEID

Dit deel beschrijft de betrouwbaarheid en reproduceerbaarheid van enkele (diagnostische) methoden, die gebruikt werden in de EMMY studie, zoals beschreven in hoofdstuk 2 tot en met 11.

De invloed van de randomisatie op de kwaliteit van leven (hoofdstuk 12)

In dit hoofdstuk werd de kwaliteit van leven (SF-36) van de deelnemers van de EMMY-studie (randomisatiegroep; n=177) vergeleken met die van de patiënten die deelname weigerden en die vervolgens behandeld werden conform hun eigen voorkeur (preferentiegroep; n=172). Bij inclusie in het onderzoek had de preferentiegroep een significant betere mentale gezondheid dan de gerandomiseerde groep (SF-36 MCS score: 46.1 vs. 41.1, $p<0.0001$). Er was geen verschil in fysieke gezondheid (SF-36 PCS: 43.7 vs. 42.9, $p=0.49$). Na 1 jaar follow-up was er geen significant verschil in mentale gezondheid tussen de twee groepen (gemiddeld verschil in SF-36 MCS: -2.62; $p=0.15$), terwijl de gerandomiseerde groep een significante verbetering in fysieke gezondheid toonde (gemiddeld verschil in SF-36 PCS: 5.97; $p=0.001$).
Blijkbaar deden patiënten met een betere mentale gezondheid minder snel mee met de EMMY studie dan patiënten met een slechtere mentale gezondheid. Voorts werd bij deelnemers aan de EMMY studie een veel sterkere verbetering in fysieke gezondheid waargenomen dan bij vrouwen die niet meededen..

Het scoren van MRI parameters (hoofdstuk 13)

De digitale MRI beelden in de embolisatie arm van de EMMY-studie werden gebruikt om de intra- en inter-beoordelaar variabiliteit te onderzoeken van diverse parameters die van

belang zijn bij de beoordeling van myomen. De beelden werden beoordeeld op twee verschillende momenten door twee verschillende radiologen die niet op de hoogte waren van de patiëntkenmerken. De overeenstemming tussen beide radiologen, bij de beoordeling van het baarmoeder volume, het volume van het grootste myoom en de locatie van het grootste myoom, was erg goed (ICC=0.99, ICC=0.98, ICC=0.88, κ=0.82). De vergelijking van beide beoordelingen door dezelfde radioloog na een tijdsinterval, toonde vergelijkbaar goede resultaten.
Concluderend bestond een goede reproduceerbaarheid van de beoordeling van MRI scans van vrouwen met een uterus myomatosus die voor embolisatie in aanmerking komen.

Vergelijken van vaginaal toucher met beeldvormende technieken (hoofdstuk 14)

In deze substudie vergeleken we verschillende methoden die in de EMMY-studie gebruikt zijn om het uterus volume (UV) te schatten: de grootte geschat met het vaginaal toucher ('Klinisch UV') en met behulp van echo-onderzoek ('Echo UV') werden vergeleken met het werkelijke gewicht van de baarmoeder, zoals gemeten direct na de hysterectomie ('Werkelijk UV') en met het geschatte volume vastgesteld met MRI ('MRI UV').
De correlatie tussen Echo UV en Werkelijk UV was goed (ICC=0.64). De correlatie tussen Werkelijk UV en Klinisch UV was redelijk (ICC=0.58). De overeenstemming tussen MRI UV en Echo UV was goed (ICC=0.75). Hetzelfde gold voor MRI UV en Klinisch UV (ICC =0.67). De overeenstemming tussen Klinisch UV en Echo UV was redelijk (ICC=0.55). Echo was superieur bij het vaststellen van UV vergeleken met vaginaal toucher. Echo was vergelijkbaar met MRI en kan daarom MRI vervangen bij de bepaling van het volume van de baarmoeder: dat is goedkoper en eenvoudiger uit te voeren.

ALGEMENE DISCUSSIE

Toen de EMMY studie opgezet werd, waren er slechts enkele kleine patiënten series gepubliceerd die een substantiële verbetering van klachten lieten zien na een embolisatie behandeling [11;16-21]. Volgens deze ongecontroleerde onderzoeken trad de verbetering van menorrhagieklachten op bij gemiddeld 85% van de patiënten.
Deze veelbelovende resultaten rechtvaardigden het uitvoeren van een gerandomiseerd onderzoek om de werkelijke waarde van deze nieuwe behandeling te onderzoeken ten opzichte van bestaande therapieën zoals hysterectomie.

Tijdens het uitvoeren van de EMMY studie werden enkele grote cohortonderzoeken (met meer dan 100 patiënten) gepubliceerd. Een verbetering van menorrhagieklachten werd gerapporteerd bij 83-88% van de patiënten [22-25].

Dergelijke hoge succespercentages werden niet bevestigd door de eerste semi-gerandomiseerde studie die 57 patiënten includeerde, waarvan 40 een embolisatie ondergingen en 17 een hysterectomie. Deze studie vond een lagere effectiviteit van 79% [26]. Hoewel de kwaliteit van deze studie slechts geclassificeerd kan worden als matig [27], suggereren de resultaten dat het succes van een behandeling ondermeer afhankelijk is van de selectie van patiënten: in deze studie waren alle patiënten geschikt om een hysterectomie te ondergaan, en vertegenwoordigden dus de categorie patiënten met de ernstigste klachten.

In de Verenigde Staten is een vrijwillige landelijke registratie geopend waarin de resultaten van 1797 embolisatie procedures geregistreerd zijn [28]. Registraties staan er om bekend dat zij een lage bewijskracht hebben (level 2c), hetgeen tot uiting komt in het extreme succespercentage van 97.1%. Een mogelijke verklaring is het niet registreren van mislukte casus en het includeren van patiënten met geringe klachten.

Embolisatie: bewijs uit gerandomiseerd onderzoek

Na de publicatie van de korte termijn resultaten van onze studie werden de resultaten van een andere gerandomiseerde studie gepubliceerd (de 'REST studie') [29]. In tegenstelling tot de EMMY studie randomiseerde de REST studie de patiënten in een 2:1 verhouding tussen embolisatie (n=106) en 'de beste chirurgische optie' (hysterectomie (n=43) of myomectomie (het verwijderen van myomen zonder het verwijderen van de baarmoeder, n=8)). De REST studie rapporteerde haar resultaten na 12 maanden follow-up, terwijl wij onze patiënten tot 24 maanden na de ingreep vervolgden. De resultaten van beide onderzoeken zijn samengevat in Tabel 1. Aangezien de REST studie soms voor een andere weergave koos (bijvoorbeeld mediaan in plaats van gemiddelde) werden onze resultaten in Tabel 1 aangepast aan de weergave van de REST studie. Dit verklaart eventuele discrepanties tussen Tabel 1 en de rest van dit proefschrift.

Klinische resultaten zoals opnameduur, duur van het ziekteverzuim, klinisch niet succesvolle procedures (beide rond 20%) en kwaliteit van leven scores zijn goed vergelijkbaar. Sommige resultaten verschillen echter. Het volume van de baarmoeder was hoger in de REST studie. De kosten werden anders berekend, hetgeen het absolute verschil in kosten verklaart tussen beide studies. Daarentegen komt het verschil in kosten wel overeen (EMMY: $1625; REST: $1712). Zoals al eerder genoemd, was de follow-up periode verschillend tussen beide studies: 1 jaar in de REST studie versus 2 jaar in de EMMY-studie.

TABEL 1. Uitkomsten van de EMMY-studie en de REST-studie

	Embolisatie		Hysterectomie*[1]	
	EMMY	REST	EMMY	REST
Patiënt karakteristieken voor de ingreep				
Aantal patiënten	88	106	89	51
Leeftijd (gemiddeld in jaren)	44.6	43.6	45.4	43.3
Baarmoedervolume (gemiddeld in cm^3)	472	579	481	701
Menorrhagie als belangrijkste symptoom (%)	100	55	100	58
SF-36 MCS (gemiddelde, range: 0-100)	42	40	41	40
SF-36 PCS (gemiddelde, range: 0-100)	44	46	44	44
EQ-5 (gemiddelde, range: 0-100)	70	**70**	68	**63**
Procedurele resultaten				
Hebben de toegewezen behandeling ondergaan (n)	81/88 (92%)	101/106 (95%)	75/89 (84%)	48/51 (94%)
Technisch mislukken van de ingreep (n)	4/81 (5%)	3/101 (3%)	0/75 (0%)	1/48 (2%)
Korte termijn resultaten				
Pijn score 24 uur na de behandeling (gemiddeld, range: 0-10)	3.1	**3.0**	3.9	**4.6**
Duur ziekenhuisopname (gemiddeld in dagen)	**2**	**1**	**5**	**5**
Weer aan het werk gaan (mediaan in dagen)	**21**	**20**	**56**	**62**
Lange termijn resultaten				
Mislukte behandeling / secundaire hysterectomie (n)	15/77 (19.5%)	18/98 (18.4%)	0/75 (0%)	0/48 (0%)
SF-36 MCS (gemiddeld na 12 maanden)	48	48	47	49
SF-36 PCS (gemiddeld na 12 maanden)	51	52	53	53
EQ-5 (gemiddeld na 12 maanden)	78	82	77	83
Kosten (in dollars) per patiënt *[2]	**6688**	**3109**	**8313**	**4811**

*[1] Of beste chirurgische optie in de REST-studie (myomectomie n=8). *[2] De kosten betreffen alleen de medische kosten binnen het ziekenhuis. Getallen die **vet gedrukt** staan, verschilden significant tussen embolisatie en hysterectomie binnen een studie. Geen statistische verschillen konden berekend worden tussen beide studies. SF-36: Medical Outcome Study Short Form-36; MCS: mental component summary; PCS: physical component summary. EQ-5: EuroQoL 5

Ook de complicaties van de EMMY- en REST-studies werden op verschillende wijzen geregistreerd en zijn daardoor niet goed onderling vergelijkbaar en worden hier derhalve niet besproken.

Uit deze gerandomiseerde studies, inclusief de eerder genoemde kleine semi-gerandomiseerde studie [26], blijkt dat het klinisch succes percentage na een geslaagde embolisatie procedure ongeveer 80% is. Dit is lager dan de eerder gerapporteerde succes percentages vanuit de cohortonderzoeken. Het verschil heeft waarschijnlijk te maken met het feit dat deze cohortonderzoeken een minder nauwgezet datamanagement hadden ten opzichte van gerandomiseerd onderzoek, dat ongunstige resultaten mogelijk niet gerapporteerd werden en patiënten geïncludeerd met een sterk wisselend klachtenpatroon [27].

De indicatie om een embolisatie uit te voeren was in de drie gerandomiseerde onderzoeken goed vergelijkbaar en de resultaten waren vrijwel identiek wat betreft succes percentages. Dit onderstreept opnieuw het belang van gerandomiseerd onderzoek bij de beoordeling van nieuwe behandelingen.

IMPLICATIES

Op basis van onze resultaten zijn wij van mening dat, wanneer een patiënt geschikt is voor een hysterectomie in verband met menorrhagieklachten bij myomen, de mogelijkheid van een embolisatie met haar besproken dient te worden. Uiteindelijk zou de voorkeur van de patiënte de doorslag moeten geven bij de behandelingskeuze.

Wij ondersteunen de implementatie van embolisatie als therapeutische optie voor symptomatische myomen in Nederland. Essentieel voor dit proces is een nauwgezette samenwerking tussen gynaecoloog en interventieradioloog, zodat een goede patientenzorg gewaarborgd wordt.

Om de implementatie te assisteren, worden richtlijnen ontwikkeld voor de Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) en de Nederlandse Vereniging voor Radiologie (NVvR). In deze richtlijnen zullen de volgende onderwerpen aan de orde moeten komen: 1) de selectie van patiënten; 2) procedurele aanbevelingen over de uitvoering van de embolisatie behandeling; 3) een adviesprotocol voor pre- en post procedurele pijnbehandeling; 4) een protocol voor de verpleegafdeling; 5) aanbevelingen voor de nazorg van patiënten; en 6) aanbevelingen voor de counseling van patiënten, inclusief een patiënten informatiefolder.

TOEKOMSTIG ONDERZOEK

In dit proefschrift werd vastgesteld dat embolisatie een goed alternatief is voor hysterectomie bij de behandeling van therapie resistente myomen bij vrouwen zonder kinderwens. Vanzelfsprekend kunnen deze resultaten niet zondermeer geëxtrapoleerd worden naar vrouwen *met* een kinderwens. In een recent verschenen review, dat embolisatie met myomectomie vergeleek bij vrouwen met een actieve kinderwens, bleek dat zwangerschap- en bevallingsgerelateerde complicaties frequenter voorkwamen bij patiënten die een embolisatie hadden ondergaan. In vergelijking met myomectomie kwamen bij zwangerschappen na een embolisatie hogere percentages vroeggeboorte (OR: 6.2, 95%CI: 1.4-27.7) en liggingsafwijkingen (OR: 4.3, 95%CI:1.0-20.5) voor [30]. Dit review betrof uitsluitend niet-gerandomiseerde studies. Gerandomiseerd bewijs ontbreekt, maar is noodzakelijk om de exacte rol van embolisatie bij vrouwen met kinderwens vast te stellen. Aangezien onze resultaten in hoofdstuk 10 impliceren dat er schade aan de eierstokken ontstaat na een embolisatie, met mogelijke consequenties voor de fertiliteit, is terughoudendheid geboden. De groep vrouwen bij wie wij schade aan de eierstokken vaststelden was relatief oud (45 jaar). Of ook bij jongere vrouwen (bij wie meestal de kinderwens nog speelt) dergelijke schade ontstaat, verdient nader onderzoek. Theoretisch zou de ideale patiëntenpopulatie voor een

dergelijk gerandomiseerd onderzoek de groep zijn die een kinderwens *en* menorrhagie heeft; deze vrouwen behoeven immers behandeling voor de bloedingklachten, waarbij hormonale medicatie geen optie is gezien de interferentie met de wens zwanger te willen worden. De ideale controlegroep zouden vrouwen zijn die voor dezelfde klachten een myomectomie ondergaan, een behandeling die ook baarmoedersparend is. Het aantal geschikte patiënten dat in aanmerking komt voor een dergelijk onderzoek is echter klein en het zou flink wat tijd in beslag kunnen nemen voordat een dergelijke studie tot een succesvol einde kan komen. Mogelijk is een internationale samenwerking noodzakelijk om deze studie te realiseren.

Verder onderzoek zou zich ook moeten richten op optimalisatie van de embolisatie behandeling, waarmee de technische- en klinische succespercentages zouden kunnen verbeteren. Zo worden micro-catheters steeds meer gebruikt, waardoor vaatspasme verminderd wordt, hetgeen de resultaten zou kunnen verbeteren [31]. Ook is het gebruik van pre-embolisatie MRA beschreven wat waardevolle informatie oplevert met betrekking tot de anatomie van de uteriene vaten. Hierdoor kunnen de technische moeilijkheden al bij voorbaat in kaart gebracht worden zodat daarop geanticipeerd kan worden [32]. Ook is het vervaardigen van een MRI scan direct na de ingreep mogelijk waardevol om eventuele myomen in beeld te brengen die ondanks embolisatie nog van bloed voorzien worden [33]; in geval van persisterende doorbloeding zou een her-embolisatie overwogen kunnen worden. Ook her-embolisaties na een niet succesvol klinisch resultaat worden steeds meer toegepast met goede resultaten in kleine ongecontroleerde series [34] en deze strategie dient nader onderzocht te worden.

Helaas hebben we in de EMMY studie geen factoren kunnen identificeren die een slechte uitkomst na embolisatie konden voorspellen (hoofdstuk 6). Mogelijk kunnen in grotere groepen embolisatie-patiënten wel voorspellende variabelen gevonden worden, waardoor de patiënten selectie en daarmee het klinisch succes verbeterd kan worden.

Tot aan de overgang kunnen myomen en daarmee menstruele bloedingklachten terugkeren of weer verhevigen. Daarom is het de bedoeling om onze patiënten groep te blijven volgen tot ze allemaal in de overgang zijn. Dit voorjaar (2007) is de eerste procedure in het kader van de EMMY-studie al weer vijf jaar geleden. In de komende periode zullen wij onze patiënten benaderen om in kaart te brengen hoe het nu met ze gaat. Wij zullen in de komende tijd de vijf jaar resultaten analyseren en publiceren.

CONCLUSIE

De EMMY studie heeft de waarde van embolisatie ten opzichte van hysterectomie onderzocht voor de behandeling van symptomatische myomen van de baarmoeder. We konden aantonen dat embolisatie een waardevol alternatief is voor patiënten die een hysterectomie moeten ondergaan voor deze indicatie. Embolisatie bleek klinisch niet-inferieur te zijn aan hysterectomie (dus klinisch onsuccesvol in minder dan 25% van de gevallen). Embolisatie was gelijk aan hysterectomie met betrekking tot kwaliteit van leven, ernstige complicaties en effect op de functie van de eierstokken. Embolisatie was gunstiger voor wat betreft de duur van de ziekenhuisopname, het herstel, en de kosten. Hysterectomie bleek beter te zijn met betrekking tot het optreden van kleine complicaties, het hemoglobine gehalte en de tevredenheid van patiënten. Aangezien de meest belangrijke klinische uitkomsten niet verschilden tussen beide behandelingen, zullen andere parameters doorslaggevend zijn in de keuze tussen beide behandelingen zoals de voorkeur van de patiënt en wellicht de kosten.

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UTERINE ARTERY EMBOLIZATION **VERSUS** HYSTERECTOMY FOR SYMPTOMATIC UTERINE FIBROIDS

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LIST OF ABBREVIATIONS

AMH	Anti-Müllerian Hormone
ANOVA	Analysis of Variance
AP	Antero-Posterior diameter
BIS	Body Image Scale
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Record Form
CIRSE	Cardiovascular and Interventional Radiology Society of Europe
DDI	Defecation Distress Inventory
DSL	Diagnostics Systems Laboratories
EMMY	EMbolization versus hysterectoMY
EQ-5D	Euroqol 5 dimension level 3 version
FSH	Follicle Stimulating Hormone
GnRH	Gonadotropin-Releasing Hormone
HRQOL	Health Related Quality of Life
HRT	Hormone Replacement Therapy
HUI-3	Health Utility Index mark 3
ICC	Intraclass Correlation Coefficient
IIQ	Incontinence Impact Questionnaire
IU/L	International Units per Liter
JR	Jim Reekers
L	Length
LAVH	Laparoscopic Assisted Vaginal Hysterectomy
LH	Laparoscopic Hysterectomy
LH	Luteinizing Hormone
LOA	Bland Altman's Limits of Agreement
MCS	Mental Component Summary (MOS SF-36)
MOS SF-36	Medical Outcomes Study 36-item Short Form health survey
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
NICE	National Institute of Clinical Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drugs
NRS	Numerical Rating Scale
PBAC	Pictorial Blood Assessment Chart
PCS	Physical Component Summary (MOS SF-36)
PVA	Polivinyl Alcohol Particles

OR	Odds Ratio
RCT	Randomized Controlled Trial
REST	Randomized trial of Embolization versus Surgical Treatment
RR	Relative Risk
SAQ	Sexual Activity Questionnaire
SIR	Society of Interventional Radiology
SD	Standard Deviation
SF-12	Same as MOS SF-36, but contains only 12 items
SPSS	Statistical Package for the Social Sciences
T	Tesla
TE	Echo Time
TR	Repetition Time
TX	Texas
TSE	Turbo Spin Echo sequence
UAE	Uterine Artery Embolization
UDI	Urogenital Distress Inventory
US	Ultrasound
USA	United States of America
UV	Uterine Volume
W	Width
κ	Kappa

CURRICULA VITAE

NICOLE VOLKERS

Nicole Aimee Volkers was born on Sunday the 29th of April 1973 in the Queen Elisabeth Hospital, Johannesburg, South Africa. Her parents' initial plan to travel overland through Africa back to Holland in a Deux Chevaux was discarded because of Nicole's South African citizenship, causing several African countries to refuse her entry. At the age of 9 months, she flew back to Holland, where her parents started on the realization of another dream: building a boat to travel the world. When she was four, the boat was ready to travel the seven seas, and they started out on the long journey to New Zealand. Due to her mother's seasickness the voyage had to be cut short in the Caribbean and Nicole started elementary school in Bonaire. When the family returned in 1980 to the Netherlands, she entered the European School in Bergen where she completed her European Baccalaureate in 1991.

In 1991 Nicole started medical school at the 'Vrije Universiteit' (VU Medical Centre) in Amsterdam together with the undersigned. As a medical student Nicole went back to the continent of her birth to carry out a research project on the communication between mothers and daughters in Uganda, on the subject of sexuality and HIV/AIDS. She got especially interested in surgery, gynecology and radiology, performing extra elective internships in these fields. In 1998 she went back to South Africa as an intern to work in the trauma unit at the G.F. Jooste Hospital in Cape Town.

After graduating from medical school in 1999 she worked as a resident Tropical Medicine (AGNIO) in the Medical Centre Molendael, Baarn and at the Department of Surgery in the St. Lucas/Andreas Hospital in Amsterdam. In 2001 she started as a research fellow (together with Wouter Hehenkamp) in the Department of Radiology at the Academic Medical Centre in Amsterdam under the supervision of prof. dr. J.A. Reekers (Department of Radiology), dr. W.M. Ankum (Department of Gynecology) and dr. E. Birnie (Department of Public Health Epidemiology). During the following four years she carried out the research presented in this thesis. During this period she presented several of the results at national and international congresses. In 2005 Nicole started her specialist training in Radiology at the Academic Medical Centre in Amsterdam (prof.dr. J.S. Laméris en dr. O.M. van Delden). She received the award for best scientific presentation at the Radiologendagen 2006.

Nicole is happily married to Gijs Nollen and proud mother of Julie and Casper.

Marieke, Orla & Tjarda, paranimfs

WOUTER HEHENKAMP

Wouter Johan Karel Hehenkamp was born -two weeks late- on March 22nd 1976 in Amersfoort. The delivery was conducted by his grandfather Karel. Two and a half years later the family welcomed Ninouk, Wouter's little sister. His grandfather was very fond of obstetrics, and because of his enthusiasm and stimulation Wouter had already decided to become a gynecologist at elementary school. In 1994 Wouter graduated from high school at the 'Johan van Oldenbarnevelt gymnasium' in Amersfoort. In his first year of study he could not enter medical school due to the numerus fixus. Instead he studied Psychology for one year at the 'University of Amsterdam'. That summer, he and a friend decided to conquer the Alps by cycling from Maastricht to Rome in three weeks. The victory of the arrival in Rome was augmented by the news that he was allowed to start medical school.

Wouter started medical school at the 'Rijksuniversiteit Leiden'. After one year he continued medical school at the 'University of Amsterdam' (Academic Medical Centre). For more than 7 years he worked as a pianist at the Okura Hotel in Amsterdam to finance his study.

His first experience with scientific research was during his study, under supervision of prof. dr. J.A.M. van der Post in the Academic Medical Centre, Department of Obstetrics and Gynecology. The use of a portable beat-to-beat blood pressure measuring device in comparison to standard sphygmomanometry in pregnancy was researched. He passed for his Master of Science in 1999, and was registered as a Medical Doctor on 22-02-2002. Directly after his study Wouter started his PhD career on the EMMY-trial, of which the results are described in this thesis. He conducted the EMMY trial together with his supervisors dr. W.M. Ankum (Department of Gynecology), prof. dr. J.A. Reekers (Department of Radiology), dr. E. Birnie (Department of Public Health Epidemiology) and of course his partner in crime during this period, Nicole Volkers. He presented several of their results at national and international scientific meetings. On October 1st 2005 he started his residency in Obstetrics and Gynecology in the 'Onze Lieve Vrouwe Gasthuis' (prof. dr. J.M.M. van Lith) in Amsterdam together with his colleague and friend, Pieternel Steures, and continued his residency as from April 1st 2007 in the Academic Medical Centre in Amsterdam (prof. dr. M.J. Heineman).

Wouter lives together with Roald Leuven in an authentic canal house in the centre of Amsterdam.

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