Randomised comparison of uterine artery embolisation (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): 5 year results.

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Competing interest statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: JGM, KGC, GDM, OW and MAL received financial support in the form of a grant to their institutions from The Scottish Government, Chief Scientist Office and LSM received payment from the University of Glasgow for the position of statistician and trial coordinator for the submitted work; no relationships with companies that might have an interest in the submitted work in the previous 3 years; JGM acted as an expert advisor to BMJ Evidence on uterine artery embolisation and JGM and MAL acted as special advisors to NICE (2010) on uterine artery embolisation.

Details of ethical approval

REC Reference Number 05/MRE00/86. Multi-Centre Research Ethics Committee for Scotland, Deaconess House, 148 Pleasance, Edinburgh, EH8 9RS.

Details of funding

Reference CZB/4/484. Chief Scientist Office, The Scottish Government, St Andrews House, Regent Road, Edinburgh, EH1 3DG.

Details of the role of the study sponsors

The funder had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. The decision to reduce the initial subject number due to slow recruitement was discussed and agreed with the funder.

Independence of the researchers from funders

All researchers were entirely independent from the funders.

Guarantor

NHS Greater Glasgow and Clyde, Research and Development Manager.

Access to data statement

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data Sharing Statement

Data sharing: no additional data available.

Protocol

The full trial protocol has been submitted to the BMJ as a supplemental file.

Trial registration details

ISRCTN.org number, ISRCTN23023665.

Randomised comparison of uterine artery embolisation (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): 5 year results.

Abstract

Objectives

To compare the long term results of uterine artery embolisation (UAE) with surgery for women with symptomatic uterine fibroids using the REST trial cohort.

Design

A pragmatic, open, multicentre, randomised controlled trial.

Setting

Secondary care. 27 participating UK centres.

Participants

157 women aged 18 and over were randomised (in a 2:1 ratio): 106 to UAE and 51 to surgery (hysterectomy 42, myomectomy 9). Those who had symptomatic fibroid(s) larger than 2 cm were candidates for randomisation. Exclusion criteria included subserosal pedunculated fibroids, recent or ongoing pelvic infection, pregnancy, severe allergy to iodinated contrast media and any contraindication to surgery.

Interventions

Surgical arm included either hysterectomy or myomectomy compared with the UAE arm which was a bilateral uterine artery embolisation.

Main outcome measures

Quality of life at 5 years as assessed by the Medical Outcomes Study 36-item Short Form General Health Survey (SF-36). Secondary measures included complications, adverse events and the need for further intervention. A cost utility analysis was also performed.

Results

There were no significant differences between groups in any of the eight components of the SF-36 scores at 5 years (minimum $p = 0.45$). For 6 of the 8 components of the

SF-36 the 95% confidence intervals exclude a mean difference in excess of 10 points. Symptom score reduction and patient satisfaction with either treatment was very high with no group difference. Major adverse events rates were similar in both groups (19% embolization and 25% surgery, p=0.40). The intervention rate for treatment failure or complications in the UAE arm increased from 13% at 12 months to 32% at 5 years. In contrast the intervention rate in the surgical arm remained at 4%. Initial cost benefit of UAE over surgery at 12 months was lost due to subsequent interventions, with treatments being cost neutral at 5 years.

Conclusions

UAE is a satisfactory alternative to surgery for women with fibroids. The less invasive nature of UAE, needs to be balanced against the need for re-intervention in a significant minority. The choice should lie with the informed patient.

Trial registration: ISRCTN.org number, ISRCTN23023665.

Funding: Chief Scientist Office (CSO), Edinburgh, Scotland

What is already known on the subject ?

•Uterine artery embolisation is an accepted alternative to surgery for women with fibroids.

•Advantages include a more rapid convalescent period and uterine preservation

•A significant minority require further invasive treatment in the first year for either complications or recurrent and persistent symptoms.

What this study adds ?

•The majority of further interventions following UAE (surgery or repeat UAE) occur beyond the first year of follow up.

~~•Further research on UAE should focus on better patient selection and outcomes.~~The apparent economic advantage of UAE at 2 years is lost at 5 years that has important implications for the health service.

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Introduction

Uterine fibroids are a common health problem in pre-menopausal women and treatment is traditionally surgical (hysterectomy or myomectomy). Since its inception in 1995[1] uterine artery embolization (UAE) has become a well established alternative treatment for those wishing to avoid surgery and preserve their uterus. The American College of Obstetrics and Gynaecology, the Royal College of Obstetricians and Gynaecologists (U.K.) and the National Institute for Health and Clinical Excellence (NICE) (U.K.) have all endorsed its safety and short term efficacy with the caveat that longer term outcomes are required.

The randomised trials comparing UAE with surgery have all reported short term outcomes[2,3,4,5] but long term clinical data have only recently been published.[6] The clinical findings show some similarity with our data but this paper does not include an economic analysis

The aim of this study is to provide 5 year clinical and economic outcomes of the REST trial (uterine-artery embolization versus surgery for symptomatic uterine fibroids) cohort and to determine whether the previously published early results are durable.[4] This will allow a more effective comparison of UAE with surgery and provide vital information to doctors, patients and health care providers.

Methodology

Trial Design

The REST trial commenced in November 2000 in seven Scottish hospitals but later expanded to include a total of 27 centres, including two in England.

Ethics committee approval was granted by the Multicentre Research Ethics Committee and local approval granted at every centre. A trial coordinator was appointed to supervise the trial and 4 research nurses covered the 27 sites together with a research fellow in gynaecology.

A randomised parallel group study was carried out. Patients were randomised according to a computer generated (permuted blocks) schedule held by the study coordinator. Randomisation used a 2:1 ratio with twice as many subjects being allocated to the new treatment (UAE). Randomisation was stratified by centre and was done centrally by the trial coordinator once the entry criteria had been confirmed and baseline data submitted. The trial randomised 157 women with symptomatic fibroids to either UAE 106, or surgery 51 (hysterectomy 42, myomectomy 9).

The 12 month results were completed in September 2005 and have been published.[4]

The patients were followed annually for a further 4 years, collecting all the original outcome measures, which was funded as a separate grant from the CSO.

Participants

Patients were recruited at the local gynaecology clinics. Women at least 18 years old were eligible if they had one or more fibroids of more than 2cm in diameter that could be adequately imaged using magnetic resonance imaging (MRI) and causing symptoms (such as menorrhagia or bulk symptoms) and were considered by their gynaecologist to justify surgical treatment. Exclusion criteria included a contraindication to MRI, severe allergy to iodinated contrast media, subserosal pedunculated fibroids, recent or ongoing pelvic inflammatory disease and any

contraindication to surgery. There was no upper limit on the size or number of fibroids.

Data were collected by a research coordinator using a combination of postal questionnaires and telephone contact. Outcomes were recorded annually after the first 12 months up to 5 years following treatment.

Interventions

Experienced interventional radiologists carried out the embolisation procedure with referral to specialist centres from peripheral units where required. Hysterectomy and myomectomy were carried out at each local centre. The method of hysterectomy and myomectomy was left to the discretion of the operator and was not prescribed. Similarly the precise technique for embolisation was left to the operator but both uterine arteries had to be embolised and the particle size of the embolic agent standardised at 500-710 microns.

Outcome measures

The primary outcome measure was quality of life (QoL) as assessed at 1 year on the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) with scores ranging from 0 to 100, higher scores indicating better health-related QoL. The primary outcome measure and all the secondary outcomes were re-evaluated at 5 years (forming the content of this report). Secondary outcomes included the EuroQol-5D questionnaire, an 11-point symptom score, ranging from -5 (markedly worse) to +5 (markedly better), a satisfaction score (measuring whether patients would recommend the procedure to a friend), complications, adverse events and the need for

further intervention for treatment failure. Follow up intervals were 1, 6, 12, months and annually thereafter.

Complications and Serious Adverse Events

All complications were graded using the Society of Interventional Radiology (SIR) classification as shown below.[7]

Categories 1-2 were subsequently grouped as minor and 3-5 as major complications. Three of the investigators (two gynaecologists and a radiologist) independently categorised the grades of complications. In cases of non-agreement the worse grade was used. Most discrepancies were of one category.

Society of Interventional Radiology Complication Grading:

1 No therapy, no consequence
2 Nominal therapy, no consequence, includes overnight admission for observation only
3 Requires therapy, minor hospitalisation (<48 hours)
4 Requires major therapy, unplanned increase in level of care, prolonged hospitalisation (>48 hours)
5 Permanent adverse sequelae

If a complication included death, life threatening events, initial or prolonged hospitalisation, disability, congenital anomaly or intervention required to prevent permanent impairment or damage, then it was logged as an adverse event. All category 3-5 complications were recorded as adverse events.[8]

Further Intervention for Persistent or Recurrent Symptoms

Further interventions required for persistent or recurrent symptoms are different for each arm of the trial. In the UAE arm, it included repeat UAE and therapeutic surgery (e.g. hysterectomy, myomectomy and endometrial ablation). In the surgical arm, it could include removal of cervical stump (following subtotal hysterectomy), repeat myomectomy and endometrial ablation (following myomectomy).

Ovarian Failure

This was defined by a level of follicular stimulating hormone (FSH) > 40 IU/L and was assessed pre-treatment and up to one year after both UAE and surgery. These results have been published elsewhere.[9] In women of the age of those in this study, further follow up with hormone assessment was unlikely to provide additional useful information.

Sample Size

The original power calculation required a total study size of 200 participants to give 90% power to detect at the 5% significance level a difference of 10 points in the SF-36 score at 12 months (the primary endpoint). This calculation took account of the baseline adjustment and the unbalanced randomisation. It was subsequently agreed to reduce the power to 80%, which required a total sample size of 150 participants. This decision was taken in consultation with the main trial funder, in view of the slow initial recruitment rate.

An independent data monitoring committee reviewed the accumulating results and any SAEs on an on-going basis. They followed the highly conservative 'Peto'

approach to guide any recommendation to terminate the trial prematurely. Stopping rules did not need to be implemented.

Statistical methods

Analysis was by intention to treat. The quality of life scales (SF-36 and EuroQol) were analysed using analysis of covariance to adjust for baseline values. Other comparisons between groups used a two sided Student's t-test for continuous data and Fisher's Exact test for categorical data. A Kaplan-Meier survival curve was used to look at the time from initial treatment to further intervention for treatment failure and complications.

Economic analysis

Data on total resource use were collected prospectively up to five years post randomisation. This included total length of initial hospital stay, outpatient visits, visits to general practitioners and other hospital visits associated with further intervention (UAE, hysterectomy, hysteroscopic-assisted removal of expelled fibroid, other gynaecological procedures and associated complications). Unit costs for all resources used were obtained from routinely collected data and published literature. These were applied to the resource use to determine the direct healthcare costs associated with each patient from the perspective of the NHS. All costs were calculated at 2008 values (UK £). Patient-specific quality adjusted life years (QALYs) were estimated from patient responses to the EuroQol-5D questionnaire using a standard weighting process.[10] The mean costs and QALYs gained were calculated for the overall five-year period. All costs and QALYs were discounted at 3.5% as

recommended by NICE.[11] The 95% confidence intervals for the difference in mean costs and QALYs were estimated using bias-corrected and accelerated bootstrap methods. In addition, sensitivity analysis was also carried out on key unit costs by varying one component at a time.

Results

The original trial randomised 157 women to UAE (106) and surgery (51) between 2000 - 2004. The groups were well matched at baseline (Table 1).

Table 1. Baseline comparison of the two treatment groups

Table 1 Baseline comparison of the two treatment groups

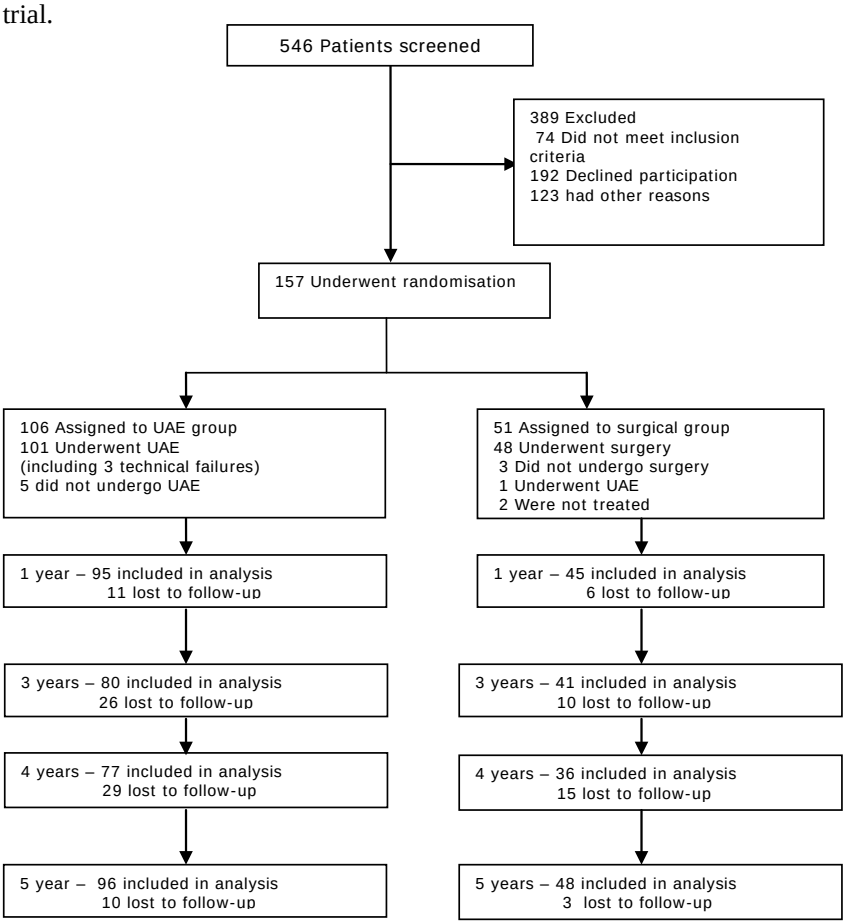
	Embolisation			Surgery		
Variable	**N**	**Mean**	**StDev**	**N**	**Mean**	**StDev**
Age (years)	104	43.6	5.5	50	43.3	7.1
Largest fibroid diameter (cm)[1]	100	7.5	3	48	8.5	3.9
Uterine volume (mls)	98	579	447	48	701	627
SF-36[2]						
physical function	104	82	19	50	77	20
role- physical	104	51	41	50	45	42
bodily pain	104	52	22	50	50	22
general health	104	61	19	50	60	23
vitality	103	41	22	50	42	23
social function	104	63	27	50	58	30
role- emotional	104	60	43	50	57	43
mental health	103	63	18	50	63	22
EuroQol	103	70	16	50	63	20
Main symptom:						
Bleeding	56	55%		29	58%	
Pain	19	19%		7	14%	
Pressure	23	23%		12	24%	
Other	4	4%		2	4%	
Total	102			50		

[1]13/148 patients (9%) had largest fibroid of less than 4cm diameter and 2/148 patients (1%) had largest fibroid of less than 3cm diameter.
[2]SF-36 and EuroQol range from 0 (worst possible) to 100 (best possible).

Eight patients (5%) did not receive their allocated treatment (five did not receive UAE and three did not receive surgery). There was one technical failure in the surgical arm with a myomectomy being converted to hysterectomy due to technical difficulties. Three patients in the UAE arm had a failed procedure due to difficulty identifying or catheterising one or both uterine arteries. Two subsequently underwent a hysterectomy and one had no further treatment. All the hysterectomies and myomectomies were performed through an abdominal incision.

The five year follow up study was completed in 2009. Only 10 (10%) (UAE group) and 3 (6%) (surgery group) were lost to 5 year follow up (Figure1).

Figure 1. CONSORT diagram showing the enrolment and follow-up for the REST trial.



Primary Outcome

The primary outcome measure (the SF-36 health-related QoL score) was available for 138 of the 157 women (88%) at 5 years. The results of the SF-36 and Euroqol-5D at 3, 4 and 5 years are shown in Table 2. There were no significant differences between groups in any of the components of the QoL measures. For 6 of the 8 components of the SF-36 the 95% confidence intervals exclude a mean difference in excess of 10

points. Both treatment arms showed a gain in QoL to reach levels comparable with age matched normative QoL SF-36 data (Figure 2).

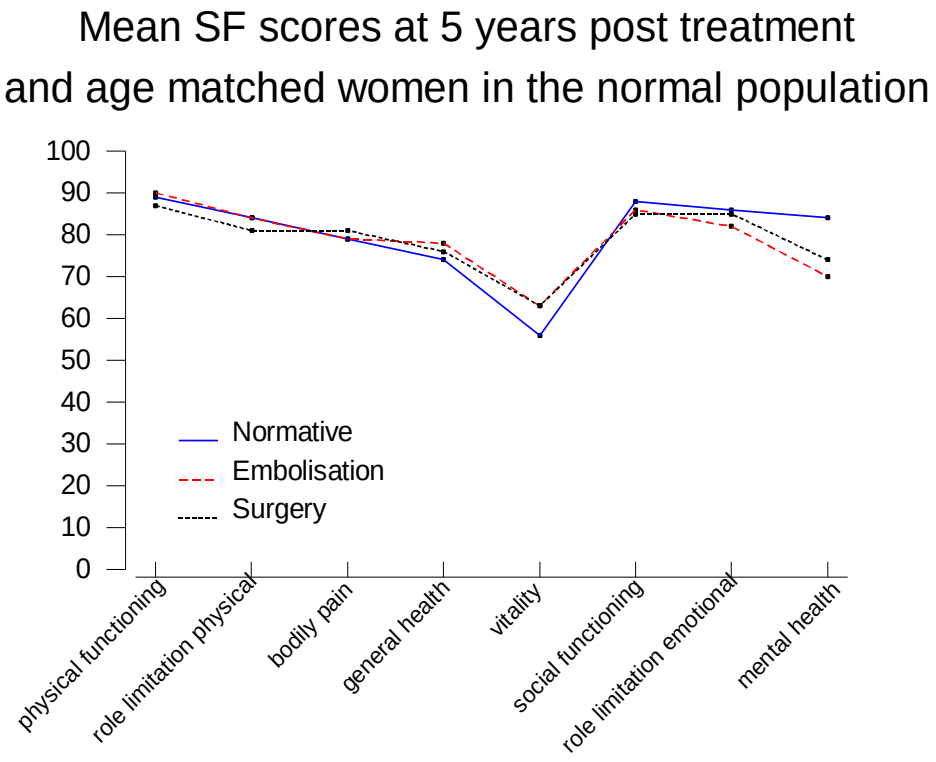


Figure 2 shows the mean score for each of the eight domains of the SF-36. There are no differences between the two arms which both closely match the normative data for healthy women of this age group in the UK. Scores for the SF-36 range from 0 (worst possible) to 100 (best possible).

Secondary Outcomes

At 5 years the mean symptom score (-5 markedly worse to +5 markedly better) was +4.5 in the UAE group and +4.8 in the surgical group (p=0.08). The percentage of

women who reported that they would recommend their treatment to a friend, was high in both treatment groups (90% in the UAE group and 87% in the surgical group, p=0.56). (Table 2).

Table 2. Effects of uterine-artery embolization and surgery on measures of quality of life (SF-36, EuroQoL), symptom score and patient satisfaction at 3, 4 and 5 years.

	UAE (E)		Surgery (S)		Difference between groups (S - E) accounting for pre-procedure levels [2]		
	Mean	SD	Mean	SD	Difference	95%CI	p

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	UAE (E)		Surgery (S)		Difference between groups (S - E) accounting for pre-procedure levels [2]			
	Mean	**SD**	**Mean**	**SD**	**Difference**	**95%CI**		**p**
3 Year SF-36 [1]	**N=79**		**N=40**					
physical function	91	16	89	22	1	-4 to	7	0.64
role- physical	86	31	84	33	0	-12 to	12	0.99
bodily pain	78	23	81	27	4	-5 to	13	0.39
general health	80	18	79	23	0	-7 to	7	0.97
vitality	69	20	66	21	-3	-10 to	5	0.49
social function	90	18	87	26	-2	-9 to	6	0.65
role- emotional	86	31	88	30	2	-9 to	14	0.68
mental health	79	16	78	19	0	-6 to	6	0.99
4 Year SF-36 [1]	**N=70**		**N=36**					
physical function	92	15	93	15	3	-3 to	8	0.34
role- physical	89	27	92	25	2	-8 to	13	0.67
bodily pain	80	21	82	22	3	-5 to	11	0.45
general health	80	17	78	23	-1	-8 to	6	0.72
vitality	66	20	66	22	-3	-10 to	5	0.49
social function	88	18	89	23	1	-6 to	9	0.69
role- emotional	86	28	88	28	1	-10 to	12	0.90
mental health	78	18	78	18	0	-7 to	6	0.90
5 Year SF-36 [1]	**N=94**		**N=44**					
physical function	90	18	87	24	0	-7 to	6	0.96
role- physical	84	32	81	36	-2	-14 to	10	0.71
bodily pain	79	22	81	27	2	-6 to	10	0.59
general health	78	19	76	24	-1	-8 to	6	0.76
vitality	63	22	63	25	-1	-9 to	7	0.84
social function	86	23	85	29	1	-7 to	10	0.81
role- emotional	82	35	85	34	4	-9 to	16	0.57
mental health	76	17	74	24	-2	-9 to	4	0.45
EuroQoL [3]								
3 Year	87	11	84	17	-1	-6 to	4	0.56
4 Year	87	11	83	16	-2	-7 to	3	0.39
5 Year	85	13	80	20	-3	-9 to	3	0.29

Table 2 continued.

	UAE		Surgery				
	Mean	**SD**	**Mean**	**SD**	**Absolute difference**	**95% CI**	**p**

Symptom score [4]								
3 years	4.3	0.2	4.7	0.1	-0.4	-0.8 to	0.0	0.04
4 years	4.4	0.2	4.6	0.2	-0.2	-0.7 to	0.3	0.42
5 year	4.5	0.1	4.8	0.1	-0.3	-0.6 to	0.0	0.08
Recommend to friend [5]	**yes**		**yes**		**(S - E)**			
3 years	58/68	85%	30/35	86%	0%	-14% to	15%	0.95
4 years	58/63	92%	22/27	81%	-11%	-27% to	6%	0.20
5 year	84/93	90%	40/46	87%	-3%	-15% to	8%	0.56

[1] Scores for the SF-36 range from 0 (worst possible) to 100 (best possible)

[2] For the differences in quality-of-life scores (on the SF-36 and EuroQol) between the surgical group and the UAE group, the analysis of covariance is adjusted for baseline values, so the differences between the groups are not simple numerical differences. Negative values indicate higher scores in the UAE group, and positive numbers indicate higher scores in the surgical group.

[3] Scores on the Euroqol range from 0 (worst possible) to 100 (best possible)

[4] Symptom score (-5 (markedly worse) to +5 (markedly better)

[5] Patient satisfaction – recommend to a friend, yes/no

Minor Complications

A total of 82 minor complications were reported over the 5 year period (20 surgical, 62 UAE). Minor complications were reported more frequently in the first year (in the surgical group 10 (20%) women reported 16 complications while in the UAE group 36 (34%) women reported 50 complications).[4] There were few minor complications reported in the 1-5 year period. In the surgical treatment group 4 (8%) women reported 4 complications (1 vaginal discharge; 2 urinary symptoms; 1 proteinuria/pyrexia) compared with 12 (13%) reporting 12 complications in the UAE arm (4 vaginal discharge; 2 abdominal pain; 2 urinary symptoms; 4 other).

Major Adverse Events and Complications

A total of 33 major adverse events and major complications were reported over the 5 year period (13 (25%) surgical, 20 (19%) UAE) and rates were similar in both groups

(p=0.40). Most of these occurred in the first year with 10 (20%) women in the surgical group and 13 (12%) in the UAE group. Between one to five years 3 (6%) in the surgical group reported a major complication and 7 (7%) in the UAE arm). (Table 3).

Table 3. Major adverse events, complications and further interventions.

	Surgery	**Embolisation**
Major adverse events and complications		
Up to 1 year	**10**	**13**
	1 Wound exploration under general anaesthetic	1 Severe vasovagal event
	2 Operative haemorrhage	2 Pain and infection requiring re-admission
	2 Anaesthetic complications	3 Pain and fibroid expulsion at 3, 4 and 6 weeks
	3 Wound infection	1 Haematometria (6 months untreated) then hysteroscopic endometrial ablation at 15 months
	1 Wound haematoma	1 Severe persistent pain requiring hysterectomy
	1 Urinary retention	1 Pelvic abscess requiring hysterectomy
		2 Temporary amenorrhea
		2 Breast cancer
1 – 5 years[1]	**3**	**7**
	1 Death – motor neurone disease	1 Death – adrenal cancer
	1 Anal sphincter repair	1 Blood transfusion
	1 Urinary tract infections	2 Severe persistent pain, 1 requiring hysterectomy
		1 Severe persistent pain and fibroid expulsion at 13 months
		1 Laparoscopy and hysteroscopy
		1 D & C
Further intervention for persistent or recurrent symptoms		
Up to 1 year	**1**	**12**
	1 Operative complication (myomectomy to hysterectomy)	3 Technical failure of procedure
		4 Repeat embolization
		5 Hysterectomy[2]
1-5 years		**17**
		4 Repeat embolization
		13 Hysterectomy

[1] After 1 year all deaths and only adverse events considered to be related to treatment are included in the table. In the embolization group there was also 1 cholecystectomy, 1 femoral hernia repair, 1 bowel polyp excision, 1 bowel resection for Crohn's disease. In the surgery group there was also 1 cholecystectomy.

[2] Includes 1 woman who also had a repeat embolization and 2 who were not embolized after randomization but subsequently had surgery (1 myomectomy , 1 hysterectomy)

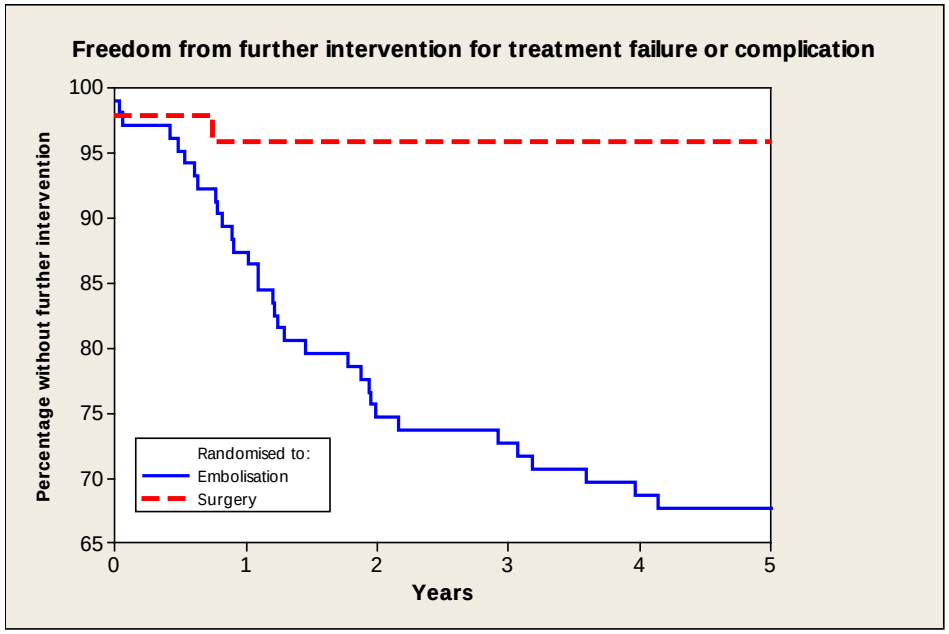
Further Intervention for Persistent or Recurrent Symptoms

Eleven patients (10%) in the UAE group and one (2%) in the surgical group had a further intervention for further symptoms during the first 12 months of the study, the details of which have been previously reported.[4] At 5 years a further 17 (16%) patients in the UAE group had either a repeat UAE (4) or a hysterectomy (13). There were no further interventions in the surgical arm beyond 1 year. (Figure 3).

The Cumulative Risk for Further Intervention

The cumulative risk for further intervention includes both those for recurrent symptoms and complications/SAEs and is probably more useful information for individual patients to understand. The cumulative risk for further intervention over the entire 5 year period is 32% after UAE and 4% after surgery. (Figure 3).

Figure 3. Kaplan-Meier curve showing freedom from further intervention for either treatment failure or complications.



Pregnancies

Twelve pregnancies occurred in five women (2 in the myomectomy group and 10 in the UAE group). All pregnancies were planned. In the myomectomy group one patient had two elective Caesarean sections, resulting in successful live births. No peri-operative complications occurred.

In the UAE group, 4 of the 10 (40%) pregnancies resulted in miscarriage and 1 resulted in an ectopic pregnancy requiring laparoscopic salpingectomy. Four pregnancies resulted in successful live births (34, 35, 38 and 41 weeks gestation). Three were delivered by Caesarean section with one post-partum haemorrhage due to an atonic uterus and another due to a morbidly adherent placenta. In a further case, the placenta was described as morbidly adherent but delivery was not associated with excessive blood loss. One intrauterine death of the foetus occurred at 33 weeks. The birth weight of the fetus was above the 90th centile with no evidence of intrauterine

growth retardation (making placental insufficiency unlikely). No abnormality was found at post-mortem examination.

Ovarian Function after Treatment

Ovarian function after treatment was assessed by measuring gonadotrophin levels and ovarian failure was defined as an FSH in excess of 40IU/l. There were no cases of premature ovarian failure (i.e. ovarian failure in women under 40 years of age). Ovarian failure developed in a total of 16 patients (13 UAE and 3 surgery (2 myomectomy, 1 hysterectomy)) of whom 14 were aged > 45 years. Both younger patients (43 and 44 years; received UAE) and 4 of the patients aged > 45 years (all underwent UAE) had an elevated basal FSH at the time of treatment (>19 IU/l) suggesting their peri-menopausal status prior to treatment.

In regard to their bleeding pattern, follow-up review indicated that all 15 patients who experienced ovarian failure (16th patient underwent hysterectomy) had some vaginal bleeding in the year following treatment. Two women ceased to bleed within 6 months and eight patients had their final bleed within 12 months of UAE. In the course of the 5 year follow-up 26 in the UAE group ceased bleeding.

Economic Evaluation

During the year 1 to year 5 follow up, the UAE arm of this study was associated with a greater number of further interventions, and subsequent greater resource use and costs compared with the surgery arm (mean costs of £671 compared with £318). This finding is in contrast to that observed in the first 12 months when UAE was associated with substantially lower costs compared with surgery (mean costs of £1727 compared with £2673).[4] As a result, over the period from baseline to five year follow up, UAE

no longer has a cost benefit compared with surgery; the total cost associated with UAE was similar to that of surgery (difference of £554). Similarly, there was little difference in QALYs between the UAE group and surgery group for the five year period (difference of -0.02 QALYs). Sensitivity analyses for year one to year five did not alter the results when assumptions were varied around the cost of MRI and US. Increasing the cost of agent and reducing the cost of inpatient stay showed a slightly higher, now significant, mean difference between the two treatments. (Table 3).

Table 3. Economic analysis

	UAE	Surgery	Difference
Mean cost (£) per patient (Year 1 to 5) (95% CI)			
Basecase	671 (432 to 910)	318 (77 to 559)	-305 (-633 to 30)
Sensitivity analysis			
Cost of MRI & US doubled	689 (445 to 934)	319 (78 to 560)	-309 (-612 to 19)
Cost of MRI & US doubled + agent cost	709 (460 to 958)	319 (78 to 560)	-352 (-690 to -4)
Cost of IP stay reduced by 50%	601 (383 to 819)	207 (57 to 357)	-352 (-613 to -94)
Cost of IP stay reduced by 65%	580 (366 to 794)	174 (45 to 303)	-359 (-615 to -139)
Mean cost (£) and Quality Adjusted Life Years per patient (Year 0 to 5)			
Cost	2467 (2076 to 2857)	2961 (2509 to 3413)	554 (-43 to 1173)
Quality Adjusted Life Years	1.57 (1.52 to 1.62)	1.60 (1.55 to 1.66)	-0.02(-0.05 to 0.05)

MRI - magnetic resonance imaging; US - ultrasonography; IP - inpatient. Calculations were based on the following unit cost estimates: uterine-artery embolisation £1.76 per minute; surgery £3.54 per minute; embolic agent £86.31 per bottle (times four bottles); hospital stay £683 per day; MRI £243.16 per scan; US £29.09 per scan; and outpatient consultation £99 per visit. The differences in costs between the surgical and UAE group were calculated using a bootstrap method, therefore the difference between the groups are not simple numerical ones. One way sensitivity analysis were preformed on key unit-costs components by varying one measure at a time.

Discussion

The initial 12 month results of the REST trial showed no difference in the quality of life gain between surgery and UAE.[4] The 5 year results show this gain to be durable in both groups which achieved levels comparable with normative data from an age matched population. In addition, both treatments are associated with very high patient satisfaction scores of almost 90%. The symptom relief score, which was initially significantly better in the surgical arm at 12 months, continued to improve over the next 4 years in both arms of the study with ultimately no significant difference between groups. This may be related to the higher re-intervention rate (32%) in the UAE arm and possibly a further reduction in uterine and fibroid volume over time.

The re-intervention rate is significantly higher in the UAE group (32%) than the surgical group (4%) at 5 years. For the purpose of this trial re-intervention included all invasive treatments whether for complications, persistent or recurrent symptoms. Most of the re-intervention is for persistent or recurrent symptoms but we also saw 5 patients who required either hysterectomy (n=3), endometrial ablation (n=1), or D&C (n=1) for complications related to UAE. There were also 5 patients in the UAE arm that either had a technical failure (n=3) or opted to have surgery in spite of being randomised to UAE (n=2). Interestingly the re-intervention rate in the UAE arm increased from 13% at 12 months to 32% at 5 years. In contrast the intervention rate in the surgical arm remained at 4%. This is important new information when counselling patients. We found a similar trend regarding complications with the majority of the surgical arm complications occurring within the first 30 days whereas in the UAE arm most complications occurred beyond the traditional 30 day “surgical window”.

The EMMY trial (hysterectomy vs. UAE) has recently reported a 28.4% hysterectomy rate for insufficient symptom control in the UAE arm.[6] Our findings concerning the likelihood of re-intervention following UAE are similar to these. However, re-intervention following surgery was much lower in our study for reasons that are currently unclear.

The HOPEFUL retrospective cohort study reported a further intervention rate of 23% at 4.6 years[12] in the UAE group. The US fibroid registry (n=1916) followed up 1278 (67%) and reported a further intervention rate of 14% at 3 years.[13] In a non randomised study comparing UAE with myomectomy, the further intervention rate was 29% in the UAE arm and 3% after myomectomy.[14] Not all re-intervention following UAE means a hysterectomy. UAE can be easily repeated and indeed 8 of the 29 re-interventions in REST were repeat UAE procedures. Despite the high further intervention rate in the REST trial, the average patient satisfaction, symptom relief and QoL scores remain high and similar in both groups at 5 year follow up. The cause of persistent and recurrent symptoms is likely to be multifactorial. Possible mechanisms include incomplete fibroid infarction, fibroid re-growth and non-fibroid related symptoms. The latter cannot be addressed by UAE whereas hysterectomy will effectively treat all causes of heavy menstrual bleeding and pressure symptoms resulting from the enlarged fibroid uterus. Katsumori has demonstrated a clear relationship between incomplete fibroid infarction and need for further intervention. He reported a cumulative re-intervention rate at 5 years, varying from 3% (with complete infarction) to 20% (with <90% infarction).[15] The cause of incomplete infarction is poorly understood but factors such as the type of embolic agent used, embolic end point of the procedure and uterine collateral blood supply from ovarian vessels, are all likely factors.

Little is known about pregnancy outcomes after UAE and this trial was not set up or powered for this outcome. Of the 10 pregnancies in the UAE arm 4 (40%) resulted in early miscarriage with an additional ectopic pregnancy and one pre-term intra-uterine death. It is difficult to comment on these outcomes although recent publications suggest an increased incidence of spontaneous miscarriage, caesarean section and postpartum haemorrhage after UAE when compared with age-matched women with fibroids.[16] Whilst one woman delivered pre-term, there were no cases of intra-uterine growth retardation or malpresentation, which is reassuring.

There were no cases of premature ovarian failure (i.e. in women under 40 years of age) although gonadotrophins rose to post menopausal levels in a significant number of women over 45 years of age in both groups which is perhaps not surprising since FSH values increase with age. Further research is required in the group of women who wish to maintain their fertility as the possibility of embolic particles causing permanent loss of ovarian function and reserve cannot currently be excluded. A study will be required in women having the procedure prior to the age of 35 if this question is to be answered..

The initial cost benefit of UAE over surgery seen at 12 months was lost at 5 years due to the further intervention rate. The HOPEFUL study showed a similar outcome in cost effectiveness.[17]

Limitations of this trial must be acknowledged. The original target number of 200 patients was reduced to 157 owing to difficulty in recruitment. In addition, the number of women undergoing myomectomy was too small to draw any meaningful conclusions.

In conclusion, the improvement in quality of life resulting from either surgery or UAE seen at 1 year was maintained and equal in both groups at 5 years with 91% follow

up. UAE is a safe and effective technique for women with symptomatic fibroids who wish to avoid conventional surgery (hysterectomy). Its safety profile (complication and adverse event rates) is similar to surgery, with most of the complications occurring within the first 12 months. Symptomatic relief and satisfaction with treatment are excellent in both groups.

Almost a third of participants in the UAE arm required further invasive treatment. This resulted in the initial cost benefit at 1 year being lost at 5 years, with both treatments ultimately having a similar cost. The less invasive nature of UAE and its associated more rapid recovery needs to be balanced against the need for further intervention. The choice should lie with the informed patient.

Contributors

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