National Institute for Clinical Excellence Interventional Procedures Programme

Systematic review of the efficacy and safety of uterine artery embolisation in the treatment of fibroids

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Host Department

The School for Health and Related Research hosts one of the two research groups that make up the 'Review Body' for the National Institute for Clinical Excellence (NICE) Interventional Procedures Programme. The other is based in the Health Services Research Unit at the University of Aberdeen.

Contributions of the ReBIP team to this review

Elizabeth Cross and Richard Wilson were involved in scoping the review, Appendix 1. Lynda Ayiku developed and ran the literature search strategies, obtained papers and formatted the references. Patricia Coleman (PC) screened the search results, developed inclusion and exclusion strategies, quality assessment, abstracted the data, and carried out the review. PC was the substantial author of the report. Jon Nicholl provided guidance and statistical advice throughout. Marc Chattle provided administrative support.

Conflicts of interest

None

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The views expressed are those of the author and not necessarily those of the funding body.

TABLE OF CONTENTS

TABLES Page

FIGURES

APPENDICES

GLOSSARY

Adenomyosis	Presence of endometrial glands and supporting tissues in the uterus where it would not occur normally
Adnexal	Parts accessory to an organ, especially the uterus
Amenorrhoea	Absence or abnormal cessation of menstruation
Anastomosis	A connection between two blood vessels or other tubular structures, occurring pathologically through disease or operatively
Angiography	Radiography of the vessels after injection of a contrast material usually requiring percutaneous insertion of a radiopaque catheter and positioning under fluoroscopic control
Arteriography	Visualization of an artery or arteries by x-ray imaging after injection of a contrast medium
Catheter	A flexible tubular instrument to allow passage of fluid from or into a blood vessel
Dysmenorrhea	Painful menstruation
Embolisation	Therapeutic introduction of various substances into the circulation either to arrest or prevent hemorrhaging or to devitalise a structure or organ by cutting off its blood supply
Fluoroscope	An apparatus for visualising the patterns of x-rays passing through a body under examination by interposing a glass plate coated with fluorescent materials
Histology	Science of the minute structure of the cells, tissues and organs in relation to their function
Hysteroscope	Instrument to enable visual inspection of the uterine cavity
Magnetic Resonance Imaging (MRI)	Diagnostic apparatus using radio-frequency pulses and signals permitting 3-dimensional localisation of the source of the signals
Menopause	Permanent cessation of menstruation; end of natural reproductive capacity
Menorrhagia	Excessive/heavy menstrual bleeding
Morphology	Science of the structure of animals and plants
Multiparous	Giving birth at least two times to an infant, (born live or not, weighing $\geq$500 grams, or having an estimated length of gestation of at least 20 weeks)
Myomectomy	Operative removal of fibroids
Necrosis	Pathologic death of one or more cells, or of a portion of tissue or organ
Nulliparous	Never have borne children
Percutaneous	Passage through the skin of needle puncture, including introduction of wires and catheters; denoting the passage of substances through unbroken skin
Peri-menopausal	A transitional stage in female reproductive capacity including physiological changes, mainly hormonal, occurring about 2 years before the menopause and ending one year later
Post-embolisation syndrome	Pain, nausea, fever, vomiting, following embolising procedures

EXECUTIVE SUMMARY

Uterine Artery Embolisation

A systematic review of the available evidence relating to the safety and efficacy of Uterine Artery Embolisation (UAE) was carried out.

Symptomatic fibroids are a common gynaecological condition. Typically they are managed by surgical intervention: hysterectomy or myomectomy. There is no long-term effective medical treatment. UAE is another treatment option. An interventional radiologist performs the procedure. The patient is sedated, and under local anaesthetic, a catheter is inserted into the femoral artery using a bilateral or unilateral technique. Using X-ray equipment to locate the blood vessels that are feeding the fibroids, fluid containing tiny particles is injected through the catheter into the small blood vessels. The particles silt up and block off the blood supply to the fibroids causing them to shrink. Some patients may expel tissue spontaneously over time, or require hysteroscopic assistance with its removal.

UAE is used in the management of other gynaecological conditions[1]. Previously it was performed in preparation for surgical intervention for fibroids[2]. Its use as a 'stand alone' procedure for fibroids was first reported in 1995[3]. Reliable estimates of the numbers of UAE procedures performed world-wide since then are not known. A survey in 2000[4] reported that 8,500 had been undertaken in the USA. Approximately 2,050 have been performed to date in the UK, (Table 1).

Search and review process

Comprehensive searches of the relevant databases (Appendix 2) were undertaken during October and November 2003. The terms and the search strategies yielded 819 potentially relevant items. The titles and/or abstracts were scanned and 256/293 papers that contained the specific words 'Uterine Artery Embolisation' **and** 'Fibroids' (or equivalent terms) were obtained. The UK literature is summarised separately (Tables 2.1-2.4), and also included in the international review in the usual way. The indexing, filtering and quality check processes admitted thirty-nine primary papers (including 5 from the UK) for detailed review (Table 3). Three papers[46,53,77] were removed subsequently.

Summary of review evidence

One randomised controlled trial (RCT), two comparative studies, one patient questionnaire survey, and 32 papers (one reporting baseline data only) from 25 case series of patients were reviewed. Most papers were from the USA (Table 3). The number of patients in the series ranged from 11[20,76] to 555. The mean age of patients was 43 years (Tables 5-8). All the patients had symptomatic fibroids and were at the stage in their illness when some intervention was required. Beyond this, the criteria for inclusion in the UAE series varied between the studies.

Efficacy

Reductions in mean uterine volume and fibroid volume of 26-59% and 40%-75% respectively were reported in the first six months following UAE. Where longer follow up was available, the reductions continued over time in most patients (Figure 2). Greater reductions in fibroid volume were associated with larger fibroids and increased vascularity[61,63,64].

Reductions in fibroid volume has been found not to be associated with changes in symptoms[20,64]. Improvements in the symptoms, most commonly for menorrhagia, were reported in 60% to more than 90% of patients irrespective of the numbers in the clinical series (Figure 3).

The extent of any improvement in symptoms achieved is unclear. Changes in pre-treatment scores ranged from 10% to 'complete resolution'[57] were reported from smaller series of patients (range, n=11 to n=80). The largest series (n=555) reported 'marked improvements' (as distinct from 'moderate' or 'slight') for between 34% and 58% of patients. These results were based on a follow-up period of 3-months, which may not be sufficient to detect all outcomes, and they cannot be compared with the other three large series of patients (range, n=167 to n=400)[25,66,73] because differences in improvements in symptoms were not reported. Two used a simple 3-category model 'worsened', 'unchanged' 'improved'[25,73]. The third defined 'clinical failure', 'stabilisation' and 'improvement', but did not report the results for patients

(88%) whose symptoms had ‘stabilised’ and those whose symptoms ‘improved’, separately.

There was evidence that patient satisfaction was linked to clinical improvement over time. The only indicator of outcomes for a period of three years or more following UAE is based on the responses to a questionnaire survey by 51 of 57 patients who underwent UAE between three and five years previously. This reported that 61% (n=31/51) were ‘at least somewhat satisfied with their choice of procedure’

Safety

Complications were reported in between 5% and 73% of patients in the included series. This variation is likely to be affected by the size of the series, length of follow up, and how complications are defined. Pain was the most common immediate post-procedural complication. Post-embolisation syndrome (pain, nausea, fever and vomiting) is not uncommon. The main reasons for emergency surgical intervention were unremitting pain and infection post-UAE. One death was reported in an included series. Complications may occur several months after UAE usually related to late passage of fibroid tissue. The crude rates of complications in two of the larger series (>100 patients) were between 6% and 13.0%. The overall complication rates reported in the RCT for hysterectomy and UAE respectively, were 20% vs 32%. The readmission rates for the two procedures were the same (1/20 hysterectomy and 2/40 UAE); 25% of UAE patients compared to 20% of those who had hysterectomy had intra-procedural complications, and at 30 days post-procedure, 72% (29/40) of UAE patients had any complications vs. 45% (9/20) hysterectomy patients (p=0.05). The serious complication rate in the one series that defined and measured complications against an objective classification[73,74] was 1.25% (95% CI 0.3%, 2.5%).

Most studies reported a small number of cases of ovarian dysfunction either transient or permanent. The underlying mechanism for this appears to be poorly understood. One explanation is that it occurs through non-target embolisation of the ovarian arteries[56,66,70]. Several papers observed an association between permanent amenorrhoea and increasing age[54,55, 71,78].

Other issues

There were several reports of patients becoming pregnant after undergoing UAE, and delivering babies successfully[24,25,56,59]. Where stated, any pregnancy complications were not considered to be more common than in other patients of similar age and medical history.

Radiation dose and fluoroscopic times were the main focus of one paper[68] and reported in the results of four others[25,51,61,66]. Estimates of the radiation dose are reported to be higher than in other common fluoroscopic procedures, but compared to known risks associated with pelvic irradiation of other diseases, UAE was not considered by the authors to present greater risks.

Increased operator experience was associated with shorter procedure and fluoroscopic times.

Embolic particles have been found in histological examination of tissue excised from patients who have had UAE[21,50]. The significance of this for those treated successfully is unknown.

Patient satisfaction

The limited satisfaction data available is generally favourable to UAE. Several studies[54,55,76] specified the desire of some women to avoid surgery as an important factor in considering their treatment options. Two papers[47,65,] referred to the respective patient groups as highly motivated for UAE.

A patient survey of the decision-making determinants in 84 US women seeking UAE, found that published literature (not the doctor) was the primary source of information about their illness and treatment options. The three reasons for seeking UAE reported most frequently were to AVOID: 1) recurrence of fibroid symptoms (n= 80/84 95%); 2) adverse effects of other surgical treatments (n=76/84 90%; 3) prolonged recovery associated with other treatments (n=70/84 83%).

Discussion

Fibroids are a significant public health issue and there is a lot of interest in UAE from provider and patient groups in what, compared with other treatment options, is a minimally invasive procedure. The numbers of UAE procedures carried out world-wide are unknown but the patterns of publication indicate that the expertise is concentrated in a relatively small number of centres in the USA, England and France. It is estimated that no more than 1000 procedures are performed annually in the USA. Approximately 2,050 UAE procedures have been carried out in the UK to date, mostly in one centre in London and the South East (Table 1).

There is consistent evidence that UAE causes the fibroids to shrink and improvements in symptoms are reported for most patients in the short term. The limitation of the evidence is that, with the exception of one small RCT of moderate quality comparing UAE with hysterectomy, it is mostly contained in uncontrolled case series of varying size. Case series are susceptible to population bias due to selection and loss to follow up. Only one paper based on a small UK series (n=21) reported using a validated outcomes questionnaire. No consistent definitions or uniform way of measuring clinical changes in symptoms following UAE were found. The resulting variation in how the clinical data were collected and reported obscures the extent of any improvements. It prevents reliable inferences as to how efficacious UAE is and the clinical importance of any improvements, from being made. Patient satisfaction was associated with the clinical changes in symptoms achieved.

Conclusion

UAE is efficacious in that it causes the fibroids to shrink and relieves or stabilises the symptoms in 60% and >90% of patients in the short-term. The extent of any improvements gained, their clinical importance and sustainability over time, was not available from the series included in the review. The limited amount of patient satisfaction data is favourable to UAE. These data are based on selected case series, and are subject to the same reservations about their reliability and generalisability.

In respect of safety, there is weak evidence from a small moderate quality RCT that the overall rate of complications within 30 days of the procedure is similar or greater than with hysterectomy. UAE may result in a small number of serious complications in the short term[36,73,74]. The rate of serious complications following UAE available from one included series where complications were measured according to an objective system of classification, was 1.25% (95% CI 0.3%, 2.5%)[73,74].

Longer term, larger randomised controlled trials that compare UAE with other treatments for managing symptomatic fibroids in the UK population are required.

1.0 OBJECTIVE OF THE REVIEW

To systematically review the evidence for efficacy and safety of uterine artery embolisation (UAE) for the management of symptomatic fibroids.

2.0 BACKGROUND

2.1 Description of the underlying health problem

2.1.1 Epidemiology

Uterine fibroids are nodules of smooth muscle cells and fibrous connective tissue that develop within the wall of the uterus. Also known as uterine leiomyomas or uterine myomas, fibroids are benign tumours of the uterus. Fibroids are the commonest gynaecological problem in women in the UK. Asymptomatic fibroids require no treatment other than routine monitoring. Symptomatic fibroids may be associated with pelvic pain, pressure and heavy bleeding, abdominal distention and bulk-related symptoms (urinary frequency or urgency, constipation, sense of pressure). Fibroids are a causative factor in pregnancy loss[5], and may be associated with sub-fertility.

Fibroids are classified into three types:

- Intramural (growths within the walls of the uterus);
- Subserosal or subserous (growths projecting into the uterine cavity), and
- Submucosal or submucous (projecting from the outer surface of the uterus).

2.1.2 Aetiology

The aetiology of fibroids is not known, but it is believed to be associated with estrogen and progesterone because fibroids coincide with the female reproductive years. Fibroids can occur in women of any age. They are associated with excess weight, are more common in nulliparous women, and in women of Afro-caribbean ethnic origin.

2.2 Current management and alternative procedures

Symptomatic fibroids are typically managed by hysterectomy or myomectomy. Fibroids are one of the most frequent reasons for a hysterectomy. Approximately 70,000 hysterectomy procedures are performed annually in the UK and around one third will be for fibroids. There is no known long-term effective pharmacological intervention. Gonadatrophin will inhibit the growth of fibroids during the time that it is being taken. The fibroids will grow again once the treatment stops.

2.3 Uterine Artery Embolisation

2.3.1 Description

Uterine Artery Embolisation (UAE) is an alternative procedure to manage symptomatic fibroids. UAE has been used in the management of gynaecological conditions other than fibroids for some years. Previously, it was performed preparatory to surgical interventions for fibroids. The first report of UAE as a 'stand alone' procedure for fibroids was published in 1995.

UAE is performed by Interventional Radiologists using established angiographic techniques and materials to locate and place catheters into the uterine arteries. The procedure is an extension of embolotherapy used to treat postpartum haemorrhage. A percutaneous catheter is introduced into an artery using either a bilateral or unilateral technique, and manipulated under fluoroscopic guidance into the uterine arteries. When the catheters are in place, embolic particles are injected into both uterine arteries to block the blood supply. The closure of the arteries is thought to be permanent. Deprived of the arterial blood supply, the fibroids begin to shrink.

UAE takes around one hour depending on the anatomy of the patient's pelvic arteries and technical difficulty in placing the catheters.

2.3.2 Clinical indications/contraindications and putative impact

The gynaecologist and radiologist decide in consultation with the patient on whether UAE is the appropriate treatment option. Patients who have any signs of pelvic infection are not suitable for UAE. The impact of the procedure on fertility has not been established and patients who wish to become pregnant may be advised to undergo myomectomy which is not associated with a risk of ovarian dysfunction. In the immediate period post-UAE patients may experience pain, a high temperature and symptoms of what is described as 'post embolisation syndrome'. The most frequent major complication is infection. Where this cannot be managed conservatively, patients may have to undergo emergency hysterectomy.

2.3.3 Personnel - skill/experience

The patient is referred to the interventional radiologist to assess suitability for UAE by a gynaecologist. Interventional radiologists are doctors who have undergone specialist training in this type of procedure and the use of radiation. Those who have not undergone specific UAE training usually attend a centre where UAE is performed before embarking on the procedure. The interventional radiologist must be capable of percutaneous arterial puncture, safe passage of a catheter into the aorta, subselective catheterisation from the aorta to the uterine artery, angiographic imaging, embolisation with standard arteriographic catheters and microcatheters, and the subsequent assessment of the angiographic result. During UAE patients are exposed intermittently to radiation, and this requires that close attention is paid to dose limitation measures, radiation physics and radiation safety.

The nursing input in the angiography suite involves patient monitoring, control and analgesia and anti-emetics.

The management of the patient is shared by the two specialties of gynaecology and radiology.

2.3.4 Current use in the UK

The National Institute for Clinical Excellence (NICE) guidance on UAE for fibroids[6] is that there is uncertainty about the safety and efficacy of the procedure. The recommendation of a joint report published by the Royal Colleges of Radiologists, and of Obstetricians and Gynaecologists[7], was that UAE should be carried out only within the context of a clinical trial. UAE is reported to be available at 48 NHS and three private hospitals in the UK. Most of the availability is in London and the South East of England (Table 1).

Out of an estimated total of 2,050* UAE procedures for fibroids performed in the UK to date, 200 (10%) were performed outside London or the South East. Of the 1850 carried out in London or the South East, 1000 have been reported as being undertaken at one centre.

Table 1 : Reported availability of UAE by UK Health Regions*

Health Regions		Centres where UAE is available
England	North West	4
	Northern and Yorkshire	4
	West Midlands	2
	Trent	3
	Eastern	0
	London	12 (including 3 private)
	South East	14
	South West	6
Scotland		5
Wales		1
Northern Ireland		0
United Kingdom		51

*Estimates of the numbers of UAE procedures performed in the UK to date and centres where the procedure is available have been provided by FEmISA, a patient group. The data have been collated from several sources but are believed by the UK radiologists consulted to be reasonably reliable.

3.0 METHODS

3.1 Review

3.1.1 Literature Search

The aim was identify all indexed references relating to the safety and efficacy of uterine artery embolisation in the treatment of uterine fibroids in line with the agreed Scope of this review (Appendix 1). After initial piloting and discussions in a ReBIP team workshop, the search strategy and terms were refined, and a comprehensive search was carried out during October and November 2003 as follows:

Sources - 17 electronic bibliographic databases were searched, covering biomedical, health-related, science, social science, and grey literature. Additionally, the reference lists of relevant articles were checked. Selected websites were also searched for eligible evidence-based reports.

Terms - A combination of free-text and thesaurus terms were used. The 'population' terms (e.g. uterine fibroids, uterine growths, uterine tumours, etc.) were combined with the 'intervention' terms (*e.g.* uterine artery embolisation, UAE, embolotherapy, etc.). Copies of the search strategies used in the major databases are included in (Appendix 2).

No date or language restrictions were applied to the search

The searches yielded 819 items. Titles and/or abstracts were screened for inclusion and 293 reports were identified as potentially relevant. Full papers were requested. Nineteen items were unavailable in the UK. Attempted retrieval from outside the UK was not pursued. The costs of doing so could not be justified as it was unlikely to yield information over and above that contained in the items that were obtained. For the same reasons a further fifteen papers that were not retrieved routinely in the time available were not pursued. Three items obtained were clearly not relevant. The remaining 256 papers and abstracts received were indexed by country and study design, and assessed independently for relevance to the UK setting and whether they reported safety and/or efficacy.

3.1.2 Inclusion and exclusion criteria

Three priorities were identified:

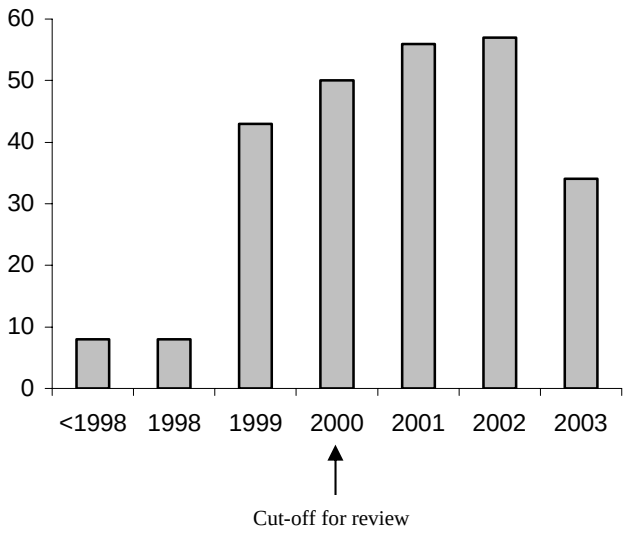
1) to capture the most recent evidence about safety and efficacy of UAE for fibroids;

2) to limit any bias due to duplication;

3) to manage the volume of literature efficiently.

The most effective way of achieving all three priorities was to use a publication cut-off date for the literature to be reviewed. Given the cumulative volume of literature it was decided that the threshold should be a publication date of 2000 or later (Figure 1).

Figure 1 Numbers of potentially-relevant publications in file (n=256)



Although there may be delays between date of study and date of publication, it was considered that as well as helping to eliminate bias that occurs when results are duplicated in multiple publications of the same data, a cut-off of 2000 would help remove any bias resulting from including results from early experiences when the technology was still developing. Potentially, adopting a 'most recent' focus would capture reports of longer-term outcomes available from revisiting treatments provided in the early stages of an 'on-going' series. It would also reduce the number of papers to one that was manageable within the time and resources available.

Multiple publications from the same patient series were only included if they reported different results, for example, clinical outcomes in one paper and quality of life indicators in another. A decision was taken not to obtain translations of 28 non-English language papers. These are listed but not otherwise considered, (Appendix 3). Five abstracts were also excluded.

The inclusion criteria used to filter the literature were:

i) Primary papers reporting on safety and/efficacy

ii) Published in 2000 or later

iii) English language

The exclusion criteria were:

i) Unavailable in the UK

ii) Not retrieved in the time available

iii) Publications of the same data reported in a later publication (and not reporting on different outcomes)

iv) Abstracts.

3.1.3 UK Literature

To help locate the results of the review within the context of the UK literature, all the papers by UK authors that were retrieved (without filters) have been indexed and tabulated separately (Tables 2.1-2.4). Correspondence by UK authors has been referenced but is not tabulated [8,9,10,11,12,13,14,15,16].

Table 2.1 CASE SERIES – UK **full papers –** No filters

Author	Purpose	Numbers Treated	Numbers reported	Age (range)	Follow up:months	Summary results
Bradley[17]	Pilot study of UAE for large symptomatic fibroids; 7 afro caribbean; 1 white	8	8	37 (31-48)	8 months	5/8 recommend UAE to others; mean uterine volume reductions; 5/8 improved symptoms; 1/8 pregnant.
Burn[18]	MRI as a predictor of outcome	18 (subset of Vashisht[24])	18	39 (28-53)	2 and 6 months	See Table 8
Burn[19]	Measures of technical success	14 (subset of Vashisht)	14	39 (31-51)	2 and 6 months	
De Souza[20]	MRI as a predictor of outcome	11	11	40	1 and 4 months	See Table 8
McCluggage[21]	Pathology of histological tissue (spontaneous expulsion or surgery) post-UAE from different institutions	10	10	42 (32-51	<0.5 to 11 months	Necrosis; giant cell reaction; foreign material elsewhere in myometrium, the cervix or paraovarian region; myometrial necrosis beyond confines of leiomyomas
Mehta[22]	Complications post-UAE	42	7	42 (31-54)	<0.25 to 7	See Table 5
Nicholson[23]	Pathology post UAE and clinical outcomes	38	38	(32-52)	1,3,and 6 months	20/38 complete resolution of symptoms; development of peripheral hyperechoic rim likely end result of PVA in peripheral arteries
Vashisht[24]	Efficacy, safety and patient satisfaction	21	21	40 (29-52)	2 and 6	See Table 5
Walker[25]	Long-term efficacy	400		43	MRI scan: 6 Ques. 1-24	See Table 5
Walker[26]	MRI changes in fibroid volume post UAE and patient satisfaction	200 (subset of Walker)	88 MR 111 ques.	43	-do-	
Watson[27]	MRI changes in fibroid volume post UAE and patient satisfaction	114 (subset of Walker)	114	42	-do-	

Table 2.2 REPORTS – UK

Author	Purpose	Conclusion/Recommendation
Joint report of the Royal College of Radiologists and Royal College of Obstetricians and Gynaecologists	Expert Clinical Opinion; Literature review of best available evidence	Subject to symptoms, treatment protocols and patient choice UAE available within a controlled clinical trial registered with a primary research programme, and using appropriate scientific methods of collecting and reporting of data; Set up a national registry to monitor UAE for fibroids, routinely.
National Institute for Clinical Excellence	Rapid appraisal of evidence	Uncertainty about safety and efficacy – Refer to Review Body for Interventional Procedures (ReBIP)
Succinct and Timely Evaluated Evidence Review (STEER)[28]	Systematic review of effectiveness of UAE	Summary of findings: Insufficient evidence of effectiveness of UAE in selected outcomes compared with alternative interventions.

Table 2.3 CASE REPORTS – UK (no filters).

Author	Age of patient	Purpose of report	Reported outcome
D'Angelo[29]	29	Spontaneous twin-pregnancy 20 months post UAE	Uneventful
Davies[30]	37	UAE complicated by endometrial ablation and Asherman's syndrome	Potential implications for future fertility:
Ellis[31]	37	Report short-term results of UAE for large uterine fibroid	Uneventful : 75% reduction in volume
Jones[32]	32-50	Six case reports: (subset of Walker)	Sequestration and extrusion of fibroid tissue post UAE patients between 20 days and 38 weeks x 6 cases: per vaginam or assisted hysteroscopic resection
Jones[33]	37	Uterine vascular supply originating from the contralateral external iliac and ovarian arteries as a cause of failure of UAE	Reason for failure of UAE
Laverge[34]	45	Spontaneous expulsion of 3 large fibroids over several months post UAE	Symptom resolution
Matson[35]	44 x 2 42 45	Four cases : 1 clinical failure 3 treatment failure	Clincial failure x 1 case: 44 years Anastomoses of the ovarian and uterine arteries x 3 cases: 42, 44, 45 years
Vashisht[36]	51	Outcome of post UAE infection (subset Vashisht)	Death : Multiparous woman (five children)
Vashisht[37]	29	Post-UAE pregnancy (subset Vashisht)	Uneventful pregnancy and elective caesarean delivery

Table 2.4 REVIEWS/EDITORIALS – UK (no filters)

Author	Purpose	Conclusion
Belli[38]	Evidence for safety and efficacy	UAE may widen treatment options for fibroids in some patients. Safety and efficacy needs to be established
Braude[39]	Clinical management	Insufficient evidence of safety and efficacy
Howatson-Jones[40]	Nursing role and standards	Nursing Care Plan based on holistic approach
Nott[41]	Safety	No clear conclusions can be drawn
Reidy[42]	Safety	Short-term results encouraging – long term safety and efficacy required; routine monitoring through national registry
Walker[43]	Safety and efficacy	UAE may be viable alternative treatment for fibroids; comprehensive data in large trials required
Walker[44]	Current debate	Summarises current issues

3.1.4 Results of filtering

The 256 items retrieved were classified broadly into primary and secondary studies. The 121 secondary papers (reviews, education and debate, reports, and editorials) were excluded. One hundred and thirty-five **primary** studies formed the initial basis of the review. The methodological quality of these was ranked according to a hierarchy of criteria of general predictive quality by specific study design, (Appendix 4). 61 items were filtered out because of incompleteness of reporting, or a publication date of 1999 or earlier, published in a language other than English or abstract only.

Thirty-five of the 74 primary papers remaining were case reports. Case reports usually describe rare events or complications. In an emerging technology they contribute to the range of clinical experiences and outcomes that may be important in considering safety and efficacy. Case reports from centres in the UK (without filters) are summarised in Table 2.3. These are presented without comment. Case reports published in 2000 and later, from outside the UK, are appended (Appendix 5.1) and referenced separately (Appendix 5.2).

3.1.5 Description of studies included

The initial inclusion criteria admitted 39 full papers based on 32 series of patients for detailed abstraction: two randomised controlled trials[45,46] (RCTs), five papers from one large multi-centre series in Canada[47,48,49,50,51], three comparative studies[52,53,54], two series in more than one centre[55,56], and 27 reports from 24 series in single institutions, five from the UK[18,20,22,,24,25] , five from other Europe[57,58,59,60,61] thirteen from North America[62,63,64,65,66,67,68,69,70,71,72,73,74,], and four from other countries[75,76,77,78,], (Table 3).

Table 3 : Included studies

UK	Country	Design	Retrospective/ prospective
Pinto	Spain	RCT (UAE v hysterectomy)	prospective
**Keyoung	USA	RCT (post UAE pain control)	prospective
Broder	USA	comparative	retrospective
Razavi	USA	comparative	retrospective
**McLucas	USA	comparative	retrospective
Pron Pron[48] Pron Colgan Pron[51]	Canada	multicentre case series	prospective
Chrisman[55]	USA	>one centre case series	prospective
McLucas[56]	USA	>one centre case series	retrospective
Ahmad	Kuwait	case series	prospective
**Bai	Korea	case series	retrospective
Banovac	USA	case series	retrospective
Bapuraj	India	case series	unclear
Burn	UK	case series	unclear
De Souza	UK	case series	prospective
Fleischer	USA	case series	unclear
Jha	USA	case series	unclear
Klein	USA	case series	prospective
McLucas		case series	prospective
Mehta	UK	case series	retrospective
Messina	Brazil	case series	prospective
Nikolic	USA	case series	prospective
Omary	USA	case series	prospective
Pelage	France	case series	prospective
Pelage		case series	prospective
Ravina	France	case series	prospective
Ryu Ryu Spies Spies[73] Spies	USA	case series	prospective
Tranquart	France	case series	prospective
Vashisht	UK	case series	prospective
Walker	UK	case series	prospective
Zupi	Italy	case series	prospective
Nevadunsky	USA	questionnaire survey	prospective

**papers subsequently withdrawn. One bias associated with early termination of study, another contained patients who did not have fibroids, and anther lacked sufficient detail.

3.1.6 Quality assessment

PC assessed the methodological quality of the 39 papers using two separate checklists that have been agreed by the Review Body to be used.

The two RCTs satisfied the 11-question checklist based on Delphi consensus methods by Verhagen[79] (Appendix 6). The 16-question checklist (Appendix 7) used to assess the quality of the remaining 37 papers was adapted from the NHS Centre for Reviews and Dissemination's guidance for those carrying out or commissioning reviews 2001[80]. The results of the quality check for the case series (n=30) which are the bases of the 37 observational papers, is contained in Table 4.

Table 4 Quality assessment of non-randomised case series (n=30)

Criteria	Yes	No	Unclear
1. (a) Where participants selected from a relevant patient population?	30	0	0
(b)Were they representative?	0	0	30
2. Were the inclusion/exclusion criteria of patients in the study clearly described?	29	1	0
3. Were participants entering the study at a similar point in their disease progression?	0	0	30
4. Was selection of patients consecutive?	12	2	16
5. Were all important prognostic factors identified?	0	0	30
6. Was data collection undertaken prospectively?	17	9	4
7. Was the recruitment period clearly stated?	16	14	0
8. Was the intervention that which is being considered in the review?	29	1	0
9. Was the Operator's experience described?	14	16	0
10. Was the place, and facilities where the patients were treated described?	19	3	8
11. Were objective (valid and reliable) outcome measures used?	29	0	1
12. Where clinical outcomes were reported?	22	8	0
13. Was the period of follow-up long enough to detect important effects on outcomes of interest?	26	2	2
14. Was information provided on all patients in the series initially?	19	7	4
15. If incomplete, were participants lost to follow-up likely to introduce bias?	0	0	11
16. Were the main findings clearly described?	25	5	0

3.1.7 Data extraction

PC was not blinded to the names of study authors, institutions, and publications. Three papers (one RCT, one comparative, and one case series) were removed following the quality check process. One RCT examined the effect of intra-arterial lidocaine for pain control following UAE. The placebo trial was predicated on an assumption that lidocaine (used for pain control in other embolising procedures) would be effective in reducing pain following UAE. The study was terminated after eighteen patients had been randomised. It was not considered further in the review. A comparative study was found to lack sufficient detail for it to be useful, and UAE in one case series was found not to have been performed exclusively for fibroids. Thirty-six papers were retained and the data were abstracted in detail.

3.2 Data organisation

The papers were separated broadly into three groups according to whether the focus was 1) 'general' i.e. reporting a range of results, or 2) 'specific' (i.e. addressing fertility issues which is a putative area of concern) or 3) relating to technological issues. Seventeen papers reported a range of results (Table 5), 7 papers addressed issues relating to fertility (Table 7), and nine papers reported technological issues (Table 8). One questionnaire survey of factors in patients' decision-making is summarised alongside patient satisfaction results available from the other studies (Table 9). One of the five papers from a Canadian study that was the largest series included ('Ontario'), reported baseline data only. All five papers Ontario papers appear in Table 6.
Individual summaries of each paper included in the review are contained in Appendix 8.

4.0 RESULTS

4.1 Summary of Evidence

4.1.1 Randomised controlled trials

The one randomised-controlled trial (RCT) compared UAE with hysterectomy. The study used a pre-consent design and was of moderate quality. Group 1 patients were randomised to be offered UAE if they agreed (n=37) or hysterectomy if they did not (n=1). Group 2 patients were intended to receive hysterectomy (n=19). Three Group 2 patients refused hysterectomy and had UAE. An intention to treat analysis was carried out to compare length of stay. However for safety and efficacy a 'treatment received analysis' was used. Forty patients received UAE. Three clinical failures converted to hysterectomy. One patient was not reported at the six months follow-up, so data were available for 36 UAE patients. Thirty-one reported clinical improvement on the primary outcome (cessation of bleeding), including six patients (17%) who had amenorrhoea. An overall success rate of 79% (n=31/39) was achieved. The reduction in the mean volume of the dominant fibroid was 46% (95% CI 27%,66%). No meaningful comparison between the efficacy of hysterectomy that has 100% effect on symptoms and fertility, and UAE, that does not, is possible.

With regard to overall safety, 32% (n=13/40) of patients made emergency department visits following UAE, predominantly for post-embolisation syndrome (n=6) or severe pelvic pain (n=3), compared to 20% (4/20) of the patients who had hysterectomy. Two/40 patients were re-admitted post UAE vs. 1/20 of the patients post hysterectomy.
25% (10/40) of the patients had intra-procedural complications during UAE vs. 20% (4/20) of the patients during hysterectomy. At 30 days post-procedure, 73% (29/40) of patients who had UAE had complications vs. 45% (9/20) of the patients who had a hysterectomy (p=0.05).

4.1.2 The Ontario (Canada) Prospective UAE multi-centre case series

Four of the five papers from a large study of 555 patients in eight centres[47,48,49,50,51] were tabulated together to provide an overview of the short-term (3 months post-UAE) results One paper reported baseline results only (Table 6). Efficacy and the effect on ovarian function in a subset of patients (n=526) who received bilateral UAE (n=538) was reported in one paper. Complications in eight patients resulting in hysterectomy were reported in another. A fourth paper reported technical results, and a fifth the results of histological examination of resected tissue from 18 patients who, underwent surgical intervention in the same 3-month period.

4.1.3 Comparative studies

Two comparative studies compared UAE and myomectomy[52,54]. Both had reviewed patient notes retrospectively. The populations of treatment groups were not similar either for age, symptoms or previous treatment. One of the studies did not attempt any case-mix adjustment, but compared symptom improvement in sub-groups reporting the particular symptom before treatment. In UAE patients 'significantly greater' ($p<0.05$) improvement was found for menorrhagia (92% vs. 64%), less 'significant improvement' was found for symptoms of mass effect (76% vs. 91%), and no statistical difference ($p>0.05$) in improvement for pain (74% vs 54%). Case-mix differences weren't taken into account in any other comparisons. The other study[54] used logistic regression to compare the need for further invasive procedures adjusting for differences in age and follow-up interval. After adjustment, the odds ratio for needing further invasive procedures in patients having UAE was 12.5 (95% CI: 1.4, 110.1). Case-mix adjustment was not used in other comparisons and the authors report that other differences could have led to bias, and that the: "…study design did not allow us to adjust statistically for those differences." The differences between the patient groups in the two studies[52,54] cannot therefore be discounted as a factor in explaining any differences in the outcomes reported. Consequently, the results for patients who received UAE have been reviewed but no further comparative data from these two studies[52,54] have been considered.

4.1.4 Case series

Thirty-two of the 36 papers reviewed were from observational case series of patients receiving UAE in one or more than one centre. One paper (Ontario series) reported baseline results only. Fifteen papers (including three from the Ontario series[48,49,51,] (Table 6) reported results across a range of symptoms and outcomes (Table 5), seven addressed issues of fertility (Table 7) and nine (including one Ontario paper) addressed technical issues (Table 8).

4.1.5 Patient survey

The results of the one patient survey included are summarised alongside quality of life and/patient satisfaction data available in the other papers reviewed (Table 9).

4.2 Study populations

4.2.1 Patients

The number of patients in the series ranged from 11[70,76] to 555. The symptoms in all patients included had reached the stage where some form of intervention was required. Some series were on-going over several years. The entry criteria for treatment by UAE varied between series. (Tables 5-8) (Appendix 8).

4.2.2 Interventional Radiologists

The focus of two studies[51,69] was interventional radiologists. One technical paper examining the diagnostic usefulness of MRI reported changes in the intentions of five interventional radiologists to treat with UAE following magnetic resonance imaging (MRI): (n=8/57 were moved to surgery). A paper in the Ontario series conducted in eight different centres reported significant differences ($p<0.001$) in both procedure and fluoroscopic times between eleven interventional radiologists with a minimum of 3-years post-fellowship experience (range 3-26 years), for successful and failed procedures (mean procedure time 61 vs 88 mins) (mean fluoroscopy time 19 vs 32 mins), and between the first 20 procedures and the next 20 procedures (mean procedure time 75 mins vs 55 mins) (mean fluoroscopy time 21 vs 61 mins).

4.3 Periods of follow-up

Diagnostic measures and clinical outcomes were reported from follow-up periods ranging from two months to more than two years. The most common period of follow up to be reported was six months. Five papers reported data in mean follow up periods of more than a year[25,52,54,57,60]. In two series[25,60], the numbers of patients lost to follow-up increased with increasing length of follow-up. The longest period of follow up was contained in a report based on a retrospective notes review and follow up survey of patients who had undergone UAE between three and five years previously.

5.0 EFFICACY AND SAFETY

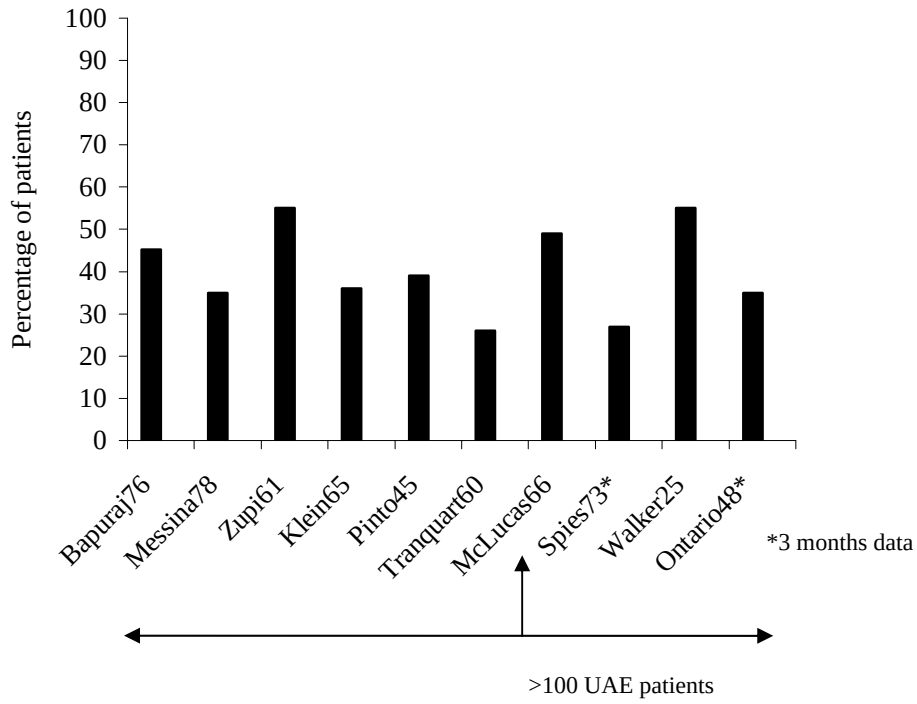
5.1 Indicators of efficacy

The measures of efficacy reported most consistently in the reviewed papers are changes to fibroid and uterine volume and impact on symptoms. The percentage reductions in mean uterine volume at six months ranged from 26% to 59%[18] (Figure 2).

5.1.1 Fibroid Volume

The range of reduction in mean fibroid volume at 6 months was 40%[64] to 75%. Where results from more than one follow-up period were available, a continuing reduction in mean fibroid volume has been reported (mean 43% (range 6%-100%) at 2 months; and mean 59% (range 6%-100%) at 6 months). One study found larger reductions to be associated with larger fibroids at baseline[48] (>400 cm^3 49% (95% CI 44%-54%)). The reverse was found in another series i.e. larger reductions (60%) associated with smaller fibroids at pre-UAE assessment of 9-108 cm^3 compared to 40% reduction in mean volume of fibroids 144-1383 cm^3 at pre-UAE assessment.

Figure 2 % Reduction in mean uterine volume at 6 months



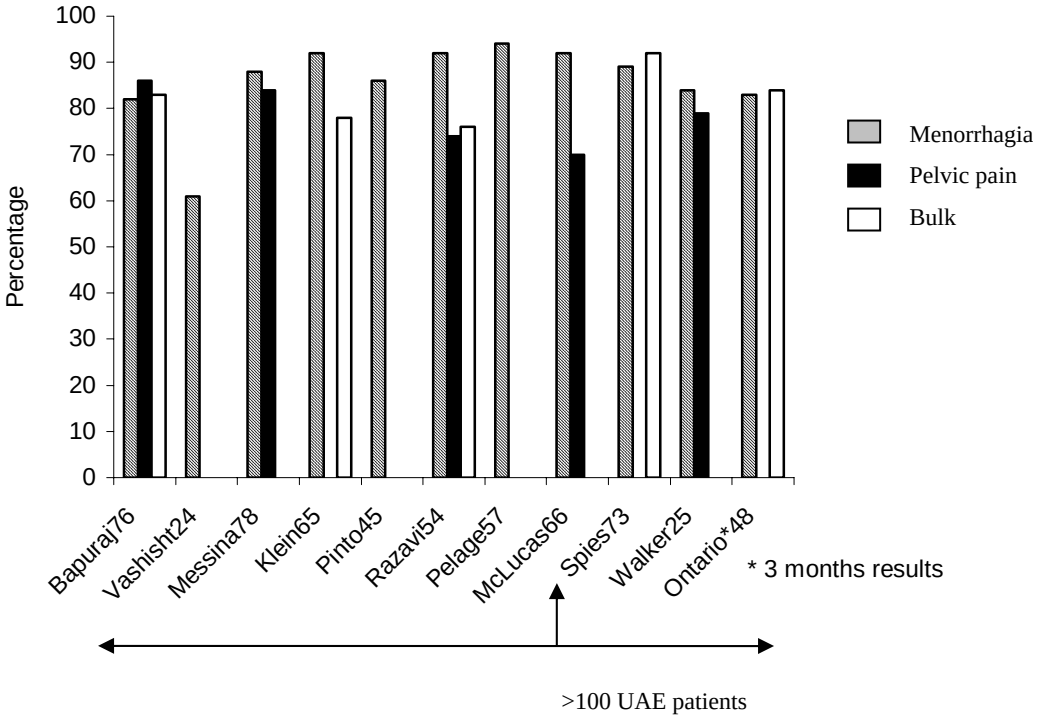
5.1.2 Symptom improvement

Short term

Seventeen of the papers reviewed reported changes in symptoms following UAE, occurring in 60% to >90% of patients[20,24,25,45,48,52,54,57,58,60,61,64,65,66,73,76,78]. Eleven reported results for specific symptoms[24,25,45,48,54,57,60,61,65,66,76]. 'Improvements' or 'stabilisation' of symptoms were reported most frequently for menorrhagia. (Figure 3).

No association was found between reductions in fibroid or uterine volume and clinical data[20,64].

Figure 3 % of patients with symptoms that improved/stabilised



Ten papers reported data on the amount of improvement in symptoms achieved [20,24,45,48,54,57,60,61,66,76]. In a series of 26 patients, changes in symptoms were classified as 'total regression, 'mild reduction' and 'no variation'. Three patients had 'no variation' in symptoms. One paper from a UK series of 21 patients used a validated outcomes questionnaire[81]. Based on 14 responses, six out of eight patients with menorrhagia (75%), and two of five patients with abdominal distention (40%) were reported as 'much better'. Seven patients were lost to follow up. Improvements over pre-treatment symptom scores in ten patients in a UK series of eleven patients, ranged from 10%-56%. Papers from two series[57,76] used the same five-point scale. For menorrhagia, one paper (n=80) reported 'complete resolution' in 72 patients and 'marked improvements' in 3 patients (the symptoms in 5 patients were unchanged). The other paper, based on a series of 11 patients reported 'complete resolution' in four patients and 'marked improvements' in five. The results at 3-months from a prospective case series of 58 patients using a 4-point scale, reported that symptoms were unchanged in 10% (n=6), improved in 76% (n=44)

and symptom-free in 14% (n=8). A retrospective review of the case notes and follow up question in 62 patients used a six-point scale. Clinical success was defined as 'complete resolution' or 'significant improvement' and successful outcomes for menorrhagia, pain and mass was reported in 92% (n=48/52), 74% (n=25/34) and 76% (n=28/37) of patients respectively. The main outcome measure in the RCT reviewed was cessation of bleeding. Success was reported for 31/39 patients. Twenty achieved 'full recovery' (56%), five 'partial recovery' (14%), and six 'amenorrhoea' (17%).

The largest prospective series of patients reviewed (n=555) reported changes in symptoms in a subset of 538 patients receiving bilateral UAE at three-month follow up based on an 'untested' 8-point scale from 'much improved' through 'no change' to 'much worse'. The symptoms of 58% of patients with menorrhagia (n=249/429), 53% with dysmenorrhea (n=170/322), 34% with bulk symptoms (n=160/464) and 53% with urinary urgency/frequency (n=163/306) were reported as 'much improved'. Three months may not be sufficient time to capture all the outcomes of interest, and data to compare these results are not available from the three other series with more than100 patients[25,66,73] in the review. One used a simple 3-category model 'improved', 'unchanged', 'worsened'. Another collected data using an 11-point scale from minus 5 (markedly worse) through unchanged to plus 5 (markedly improved), but after remodelling into an ordinal scale, the outcomes were reported as 'improved', 'unchanged' or 'worse. This paper concluded that UAE '….controls the symptoms caused by leiomyomata in most patients'. 'Clinical failure', 'improvement' and 'stabilisation' were defined in the third paper. Seven/150 patients followed up at 5 months were in the 'failure group' but results for symptoms that had 'improved' and those that had 'stabilised' were not reported separately. Although not reported expressly, one small series also implied a difference between 'stabilisation' and 'improvement'. Symptoms of menorrhagia were reported to be 'controlled' in 88% (n=21/24) of patients and symptoms of pelvic pain 'improved' in 84.2% (n=16/19).

Long-term

One paper reported 'improved' symptoms at 3 months, 6 months and >12 months follow-up in a series of n=200 women. The improvements at 3 months (heavy menstrual bleeding 87%; bulk symptoms 93%; satisfaction 93% (n=181)) were sustained at more than 12 months (90%, 91% and 92% respectively (n=167)). Two papers based on a

prospective series of more than 50 patients[57,60], reported data for different levels of improvement in follow-ups of 24 months. One reported complete resolution of symptoms in 72/80 (90%) of patients in the original series. The second reported complete resolution of symptoms in 19 of 58 patients available to follow up at 24 months. The numbers lost to follow up in this series (66%) may affect the reliability of this result.

The longest period of follow up available was a retrospective study which conducted a questionnaire survey of 51 of 57 patients who underwent UAE between 3 and 5 years previously. The only indicator of long-term efficacy reported was that 61% (n=31/51) were 'at least somewhat satisfied with their choice'.

5.2 Indicators of safety

It was not always clear whether patients had more than one complication or if the reporting of adverse effects was complete. However, the evidence reviewed indicates that crude overall rates of complications in the short-term ranged between 5% and 73%.

In the short-term post-procedure pain was commonly reported and infection was the main reason leading to emergency presentation and in some cases, emergency surgical intervention. There was one death in a UK series.

Rates of conversion post-UAE to hysterectomy couldn't be determined reliably in all the series, but on the evidence available, range between 1.3% and 11.5%. Where hysterectomy was reported and reasons were provided, three cases were related to the existence of underlying pelvic disease (other than fibroids)[66,78] which were noted before UAE. One paper reported that clinical failure of UAE was associated with previous pelvic disease or pelvic surgery.

The overall complication rates for hysterectomy and UAE respectively, reported in the RCT were 20% vs 32%. The readmission rates were the same (1/20 hysterectomy and 2/40 UAE); 25% of UAE patients compared to 20% of those who had hysterectomy had intra-procedural complications, and at 30 days post-procedure, 73% (29/40) of UAE

patients had complications vs. 45% (9/20) hysterectomy patients (p=0.05). The crossover that occurred confounds the comparative rates for complications in the two groups.

Longer term

Late passage of fibroid tissue was reported as occurring up to a year or longer after UAE[25,74]. The results of a questionnaire survey based on the responses of 51 of 57 patients undergoing UAE between 3 and 5 years previously reported that 29% (15/51) had undergone further surgical intervention. The study defined a clinical failure group as 'the need for additional invasive treatment for myomas', 'no improvement in overall symptom score' or self-rated 'dissatisfied or very dissatisfied'(Box 1). Twenty/51(39%) met these criteria.

5.3 Specific issues

5.3.1 Ovarian function and fertility post UAE

Seven papers focussed specifically on the effect of UAE on ovarian function, (Table 7). These studies are few in number and are based on series of varying size. An outcome of hysterectomy has obvious implications for fertility, and may arise following a failure of UAE, underlying disease other than myomata or unrelated to UAE. The preliminary indications in respect to otherwise successful UAE, is that incidental ovarian artery collateral embolisation during UAE may occur, and patients are counselled to the possibility of this effect.

There is evidence that ovarian dysfunction is more likely in women aged over 45 years[55,72]. The early results from the Ontario Study (excluding patients who were menopausal at baseline) also report a strong inverse association between increasing age and delay in resuming menses post UAE, (Table 6). The mechanism by which ovarian dysfunction occurs is poorly understood. Increased vascularity in older women and over-aggressive embolisation are potential explanations considered in the literature[56,62,66].

5.3.2 Pregnancy

Fibroids are not necessarily a cause of infertility but predispose to complications during pregnancy leading to spontaneous abortion and breach presentation. Occurrences of pregnancies in the period following UAE were reported[24,25,56,59]. Two series[56,59] reported a total of 29 pregnancies in 23 women, (Table 7). The complications during the pregnancies reported in the women who conceived after they had undergone UAE were not considered by the authors to be greater than in those of the same age sharing a similar disease profile and medical history generally.

5.4 Technical issues

Nine papers (including one from the Ontario trial) reported on technological aspects of the UAE including the ability of magnetic resonance imaging to predict the outcome of UAE, the effect of varying the size of the embolic particles[58, 62], and the optimum endpoint of the procedure, and operator effect (Table 8).

One paper (Ontario trial) reported the results of histological investigation of re-sected tissue in 17 of 18 patients undergoing surgery 8.2 months (median) post UAE, undertaken without knowledge of the indication of surgery or time elapsed since UAE, (Table 6). The findings were not dissimilar to those reported previously in a UK study. Embolising particles were found in the tissue. The implications of the morphologic changes observed in those experiencing post-UAE complications for those treated successfully are uncertain.

Radiation dose and fluoroscopic times were the main focus of one paper and reported in four others[25,51,61,66]. Estimates of the radiation dose are reported to be higher than in other common fluoroscopic procedures, but compared to known risks associated with pelvic irradiation of other diseases, UAE was not considered to present greater risks. Exposure time is related to procedure and fluoroscopy times.

5.5 Patients perspective/satisfaction

Nine papers reported limited data on patient satisfaction (Table 9). One paper from the USA reported factors influencing patient choice obtained in a questionnaire survey of patients previously undergoing UAE. The women believed themselves to be well-

informed about their disease and the treatment options available. Printed literature (not the doctor) was the primary source of information about UAE in 40% of the sample.

The Ontario study reported that 85% (n 414/487) were willing to undergo another UAE procedure if necessary. The figures assume that the responders are typical of the 555 recruited into the study. The proportion reduces to 65% if those who would do so only conditionally (n=93) are taken into account.

Table 5.1 Papers reporting a range of results – efficacy

Series	Country	Size	Patient descriptions	Mean Age (range)	Follow Up Months	Numbers reported	Changes in mean volume and/or symptoms
Bapuraj	India	11	Strong desire to avoid surgery	32 (28-52)	<1,2,6 months	11	2 months -10/11 clinical improvement 1-3 Pelage scale:
Vashisht	UK	21	Symptomatic fibroids	40 (29-52)	2, 6	14	Fibroid: 32.6% 2 months: 75.2% 6 months: 8/13 improved menhorrhagia; 61% 2/7 improved abdominal distension.
Messina	Brazil	26	Pre-menopausal; refused surgery	42 (33-49)	3,6,12	26	Menorrhagia: controlled 87.5%; Pain improved 84.2%
Zupi	Italy	26	Single or large myoma; intramural location; fertile age	39 (32-54)	1,3,6,12	26	Uterine: 64% 6 months; 83% 12 months; Most reduction high vascularity; Symptom improvements12/21 menorrhagia; 7/9 pain; 8/12 urinary disturbance; 18/18 abdominal weight
Klein	USA	35	Highly motivated for UAE	46 (32-56)	<2,6	30	Dominant fibroid 49% (1%,92%) 6 months
Pinto	Spain	40/57[i]	Suitable for hysterectomy; no desire for future pregnancy; fibroids <10 cm dia.	43 (18-59)	6	40	Dominant fibroid 56% (27%,66%) 6 months Improved bleeding in 31/39 patients
Mehta	UK	42	Mostly multiple myoma; 86% afro-caribbean; 9% white; 5% asian	42 (31-54)	4-16 median 12	7	No efficacy results reported
Tranquart	France	58	Symptomatic fibroids	44 (33-65)	3	58	Symptoms 10% u/changed; 76 improved; 14% resolved
Broder	USA	59/97[ii]	Previous myoma surgery; 45% white; 55% non-white;	44	37-59	51	31/51 patients some symptom improvement 61%
Razavi	USA	67/111[ii]	Strong desire to avoid hysterectomy	44	14	62/67	Symptom improvement 92% menorrhagia; 74% pain; 76% improved mass.
Pelage	France	80	Failure of hormonal treatment; menorrhagia; no desire for future pregnancy	45 (30-54)	2,6,12, 24	80	Symptom improvement72/80 complete resolution; 90% 3/80 marked improvement; 5/80 no improvement.
McLucas	USA	167	Menorrhagia predominantly	43 (29-63)	6	150	Uterine: 23% <2months; 31% 6 months; 337% 12 months. Symptom improvement/stabilisation 87% patients n=131/150. Optimum results uterus height <16 cms; slow-growing myoma without history of pelvic disease and no adnexal findings pre UAE u/sound and pelvic examination.
Spies	USA	200 (subset of	No strong desire for future pregnancy; Not pedunculated submucosal; uterus <24 weeks. 45% white; 55% non-white	43 (27-57)	12 months	158	Improved: menstrual bleeding 89%; bulk 92% at 6 months
Walker	UK	400	5/400 post menopausal; avoid difficult multiple myomectomy or hysterectomy	43(20>50)	mean 17 months	321	Latest follow up for each woman Symptom improvements 73%-90%
Ontario[47,48,49]	Canada	555	See table 6	43 (18-59)	3		See Table 6

Table 5.2 Papers reporting a range of results – safety

Series	Country	Size	Patient descriptions	Mean Age (range)	Follow Up Months	Numbers reported	Complications/events	Rate
Bapuraj	India	11	Strong desire to avoid surgery	32 (28-52)	<1,2,6	11	1 post-embolisation syndrome	10%
Vashisht	UK	21	Symptomatic fibroids	40 (29-52)	2, 6	Unclear	Pain; 1 death; 1 readmission 6 weeks for opioid analgesia	10%
Messina	Brazil	26	Pre-menopausal; refused surgery	42 (33-49)	3,6,12	26	3 hysterectomy; 3 x Ovarian failure: (1 aged <45: 2>45 years)	23%
Zupi	Italy	26	Single or large myoma; intramural location; fertile age	39 (32-54)	1,3,6,12	26	19 fever; 26 pain; 3 scanty bleeding 3 months; 2 myoma debris	
Klein	USA	35	Highly motivated for UAE	46 (32-56)	<2,6	30	1 repeat UAE; 3 surgery 4 x amenorrhoea	27%
Pinto	Spain	40/57[i]	Suitable for hysterectomy; no desire for future pregnancy; fibroids <10 cm dia.	43 (18-59)	6	40	20 moderate/major complications (excluding 6 amenorrhoea) 3 x hysterectomy.	72%
Mehta	UK	42	Mostly multiple myoma; 86% afro-caribbean; 9% white; 5% asian	42 (31-54)	4-16 median 12	7	Readmission 1-29 weeks mainly infection. 1 hysterectomy	17%
Tranquart	France	58	Symptomatic fibroids	44 (33-65)	3	58	6 unchanged	10%
Broder	USA	59/97[ii]	Previous myoma surgery; 45% white; 55% non-white;	44	37-59	51	6 hysterectomy; 8 myomectomy; 1 repeat UAE; 20/51 clinical failure	39%
Razavi	USA	67/111[ii]	Strong desire to avoid hysterectomy	44	14	62/67	1 x Pelvic pain; menopause 4 >46 years; 1 x transient numbness of groin; hysterectomy N/R	9%
Pelage	France	80	Failure of hormonal treatment; menorrhagia; no desire for future pregnancy	45 (30-54)	2,6,12, 24	80	85% intense pelvic pain; 6 amenorrhoea; 4 expulsion myoma debris; 1 hysterectomy	14%
McLucas	USA	167	Menorrhagia predominantly	43 (29-63)	6,12	150: 6 months 46 : 12 months	21 'failures' (box 1) – previous pelvic surgery or other pelvic disease. Lower success (50%) presence of adenomyosis (alone or fibroid-related);	13%
Spies	USA	400	No strong desire for future pregnancy; Not pedunculated submucosal; uterus <24 weeks. 43% white; 57% non-white	43 (27-57)	3 , 12	250 questionnaires	42 patients 47 complications ;37 x 30 days of UAE; 4 x 31-90 days; 6 .>3 months	10.5%
Walker	UK	400	5/400 post menopausal; avoid difficult multiple myomectomy or hysterectomy	43 (20 >50)	mean 17	321	23 clinical failures; 26 amenorrhoea	6.0%
Ontario[47,48,49]	Canada	555	See table 6	43 (18-59)	3		See Table 6	

i RCT, ii Comparative

Table 6 The Ontario (Canada) prospective uterine fibroid embolisation (UAE) multi-centre series

Author	Purpose	Numbers	Numbers reported	Summary results
Pron[47]	Baseline characteristics of consecutive UAE patients in 8 university and community hospitals in Canada	555	555	
Pron	3-months (ultra-sound and telephone follow up) i) clinical outcomes and ii) patient satisfaction	555	i) 526 ii) 487	Mean volume reductions in uterine and dominant fibroid of 27%-33%; fibroids >400 cm^3 50%; 83% improvements in menorrhagia, 77%; dysmenorrhea, bulk 86%. Significant improvements on impact on life scores – 72% reduced to 13% - associated with symptom relief not reductions in uterine volume. Post-UAE amenhorroea strongly dependent increasing age.
Pron	3-months results : post-UAE complications resulting in hysterectomy	555	8	i) infection; ii) post-embolisation pain; iii) vaginal bleeding; iv) prolapsed leiomyoma.
Colgan	3-months : Pathologic examination of tissue in patients undergoing hysterectomy or myomectomy following technical failure of UAE (n=10) or post UAE hysterectomy (n=8)	555	18	PVA particles in resected tissue
Pron	Effect on time of increasing numbers of UAE performed in trial. 8/11IRs at 8 centres min. 40 procedures each in trial.Performance indicator: 'Early' v 'Later' : (cut-off 20 procedures).	555 patients 11 IRs	570 procedures	Significant difference in procedure and fluoroscopic times between : interventional radiologists technical success and failure; and first 20 procedures and next 20 procedures.

Study period November 1998-November 2000

Follow up period 3-months

Patient characteristics (n=539) Mostly white (66%), 33% <30 years old; highly educated (68% graduates or postgraduate); mostly working outside homes; most used Internet; 50% no children; fertility an issue for 31%; 23% previous treatment for gynae.probs; 80% pre-menopausal; 35% overweight; 17% obese.

Symptom profile: 66% intramural fibroids; 70% multiple fibroids; average fibroid volume 293 cm^3; length 1-24 cm; average uterine volume 680 cm^3; heavy bleeding; pelvic pain; symptoms differed by age and race; non-white women more likely to have multiple fibroids; av. duration of symptoms 5-7 years.

Health status: self rated health status lower than other women of their age; 5% increased surgical risk; 19% other major health problems.

Operator characteristics: 11 interventional radiologists (IRs) in eight centres; 3-26 years post fellowship experience. 8/11 completed a minimum of 40 procedures each in trial

Table 7 Ovarian function and fertility post UAE

Series	Country	Size	Patient descriptions	Mean Age (range)	Follow Up Months	Methods	Outcome
Ryu	USA	23	1) Pre-menopausal	43 (35-51)	Baseline	Doppler ultra-sonography; Ambulatory visit; telephone survey.	In 15/17 cases evidence of incidental ovarian artery collateral embolisation during UAE ($p<0.0001$)
Ryu		6	2) Complete loss of ovarian arterial perfusion post UAE	40 (35-51)	6-7	Standardised questions	4/6 re-established ovarian arterial perfusion 1/6 had not but resumed normal menses; 1/6 (>45) developed menopausal symptoms
Ahmad	Kuwait	32	30 Pre-menopausal; 2 Peri-menopausal; no desire for future pregnancy	34 (26-45)	<1,<2,3, 6	FSH assay	Transient ovarian dysfunction in 2 peri-menopausal patients; Resumed 8-10 months post-UAE
Spies	USA	63	No strong desire for future pregnancy; Not pedunculated submucosal; Uterus size <24 weeks. 53% black; 43% white; 4% other	43 (33-50)	3,6	FSH assay; questionnaire: agegroups 30-39; 40-44; 45-50	15% risk of increased FSH levels in >45 years. Mechanism not understood.
Chrisman	USA	66	Pre-menopausal; poor candidates for surgery	(30-55)	5 <1,3,6,12	2-centre study FSH assay, Standardised questions	Ovarian failure <45 years : Nil >45 years (9/21) 43%
McLucas	USA	400		41 (26-67)	Not reported	4-centre study	Ovarian dysfunction 4 <45 premature menopause; results for >45 not reported.
Ravina	France	9*/184	Post UAE pregnancies	36*	Not reported		12 pregnancies in 9 women 4-23 months post UAE: 7 live births 3 vaginal; 4 caesarean
McLucas	USA	14/400	Post UAE pregnancies	41 (26-67)	Not reported	4-centre study	17 pregnancies in 14 women post UAE.

Table 8 Technological issues

Series	Country	Size	Participant descriptions	Mean Age (range)	Technology	
de Souza	UK	11	Menorrhagia	40 (29-48)	Correlation between volume changes and clinical outcomes	Reduction in volume on MRI does not predict clinical response changes in symptom scores
Burn	UK	18	Otherwise considered for surgical resection	39 (28-53)	-do-	MRI can predict response to UAE
Pelage	France	20	Menorrhagia; pre-menopausal; Pelvic pain; no desire for future pregnancy 15 white; 5 non-white	43 (36-53)	Effect of embolising agent on post UAE pain and non-target embolisation	Results of tris-acryl encouraging. Controlled trials required.
Fleischer	USA	20	Symptoms 6 months to one year duration	43 (38-57)	3-d color Doppler sonography to identify fibroids of different size and vascularity	Reductions in volume preceded by reduced vascularity. Hypervascular fibroids greater reduction than isovascular or hypovascular.
Nikolic	USA	20	N/R	44 (30-53)	Radiation effects	Mean UAE dose >common fluoroscopic procedures. Compared to known risks associated with level used in irradiation of other pelvic diseae unlikely to result in radiation injury or genetic risk to future children.
Banovac	USA	23	Multiple fibroids	42 (28-52)	MRI and Tris-acryl Gelatin Microspheres	Endpoint: resistance before statis – 'pruned branch appearance' Confirms previous findings[82] - agent appears safe and efficacious. Controlled trials needed
Jha	USA	31	N/R	45 (31-54)	MRI as a predictor of outcome	Useful for quantifying signal intensity and morphologic changes pre and post UAE
Omary	USA	60 5	Patients Interventional Radiologists	44 (31-54)	MRI to improve diagnostic confidence	MRI significantly altered diagnoses and treatment plans of IRs evaluating patients with presumed symptomatic fibroids
Ontario[51]	Canada	555	See table 6	43 (18-59)	Effect of operator experience in trial for UAE procedure times	See Table 6

Table 9 Patient views/satisfaction

Series	Country	Size	Measure of satisfaction	Mean Age (range)	Follow Up Months	Numbers Reported	Results
Vashisht	UK	21	Would you recommend UAE to a friend?	40 (29-52	6	14	7 definitely; 2 probably; 4 unsure; 1 No
Klein	USA	35	'subjective satisfaction (not otherwise reported) and not seeking further therapy'	46 (32-56)	6	30	26 very satisfied : 4 unreported
Pinto	Spain	40/57[i]	Would you undergo the same treatment again?	43 (18-59)	6	36	28 yes; 5 no; 3 maybe
Broder	USA	59/97[ii]	Not reported	44	37-59	51	31 at least somewhat satisfied (61%)
Nevadunsky	USA	84	Questionnaire survey of factors in decision in women undergoing UAE; all candidates for surgery; 71% white; 70% college degree or higher; 70% household income >$50,000 - (socio-demographic atypical of New Jersey population).	44 (27-56)	Unclear	84	Fibroids significant impact on lifestyle; Literature primary source of information about UAE. Decision determinants in >50% of responders; 1) avoid recurrence of symptoms; 2) avoid adverse effects of alternatives; 3) avoid prolonged surgical recovery; 4) avoid surgery
McLucas	USA	167	Would you recommend UAE to others?	43 (29-63)	6	150	87% (n=130) yes
Spies	USA	200	Linked to categories of clinical outcomes	43 (27-57)	3 , 12	158	6 months (n=158)'satisfied' 93%
Walker	UK	400	Would you choose UAE again? Would you recommend UAE to others?	43 (20 >50)	24	131	97% (n=127) yes
Ontario	Canada	555	Satisfaction scale: willingness to undergo another UAE and overall satisfaction verbal score 1-6 (greatly; moderately; mildly [dissatisfied]; mildly; moderately; greatly [satisfied].	43 (18-59)	3	487	91% satisfied (mildly; moderately; greatly) 85% (414) willing to undergo UAE again, (93/414) only conditionally so.

i RCT
ii Comparative

5.6 Limitations of available evidence

An important limitation of the evidence reviewed is that, apart from a small RCT of moderate quality, it is contained in uncontrolled case series that are susceptible to population bias. Additionally, changes in symptoms are based on self-reported changes assessed on ordinal scales ranging from 3 to 11 points[73] (Box 1), that have not been tested. Reference was found to a new symptom-specific and quality of life instrument for fibroids[83]. This was not used in any of the studies reviewed. Only one paper reported using a validated outcomes questionnaire. This reported improvements in menorrhagia for a lesser proportion of patients than other studies (61% vs. ≥82%) (Figure 3) and the reliability of these data are affected both by the small size of the series (n=21) and patients lost to follow up (n=7/21).

Ten series ranging in number from 11[20,76] to 80[57] reported on the amount of improvement in symptoms. There was substantial variation in the amount of improvement in symptoms that were quantified (improved score of10% to 'complete resolution'). The differences in the amount of improvement for patients whose symptoms had 'improved', and those that had 'stabilised'[66], or were controlled was unclear, as was the clinical importance of any changes in symptoms.

Reliable long term data are not available, either because these have not yet been reported[47,48,49] or patients are lost to follow-up[25,66,73].

The overall complication rate observed ranged between 5% and 73%. The rates available in papers from the larger series reviewed are within this range, (6%[25] and 13%). The wide variations in the smaller series will be due to the size of the series, and differences in how complications are defined and reported. The overall rate of complications in two papers from a series that used objective standardised measures to classify complications within the first 30 days following UAE[73,74] was 10.5%. The rate for major complications was 1.5%.

Comparison of results will be affected by different lengths of follow up. The largest series (n=555) and one of the smallest series (n=11) reported clinical results obtained in follow-ups of 3 months or less. This is unlikely to be sufficient to capture all the changes in symptoms or adverse effects that may occur.

The results reported also assume that patients lost to follow-up are the same as those still available[52,60], and this assumption may not be valid.

Patient satisfaction data were limited. Those linked to clinical outcomes are subject to the same reservations as to their reliability and generalisability

Box 1 : Outcome measures

Broder[52] 7 point scale of clinical improvement and 4 point scale for patient satisfaction from very satisfied to very dissatisfied; (inclusive) Clinical failure: need for additional invasive treatment for myomas or no improvement in overall symptom score or self-rated dissatisfied or very dissatisfied.

McLucas 3-point Pre-UAE symptom scale: severe,moderate,mild. Post UAE 'improvement' moving from severe to moderate; 'stabilisation' moderate or mild. 'Failure group': 1) hysterectomy or 2) <10% shrinkage of myoma at 6 months; or worsening symptoms.

Pelage[58,76]scale: 5 point scale: 1) complete resolution to 5) worsening;

Razavi 6-point scale: 6) complete resolution to 1) significantly worse. 'clinical success' = 5 or 6.

Spies collected on 11-point scale 'minus 5 markedly worse thru 0 to plus 5 'markedly improved' reported as improved; unchanged; worsened. Patient satisfaction data were collected and reported in the same way.

Spies standard measures of complications based on service use developed by Society of Cardiovascular and Interventional Radiology Complication Class (SCVIR); and criteria of the American College of Obstetricians and Gynaecologists (ACOG).

Vashisht validated Menorrhagia Outcomes Scale

Walker pain score: 8 levels: no pain to worst pain ever felt;
3 level symptom scale: improved-unchanged-worsened;
Patient satisfaction indicator: recommend UAE to others.

Ontario[47,48,49] (rating scale was not tested)
1) life impact score;
2) 'willingness to undergo another UAE if necessary'; and
3) 6 point scale satisfaction scale

6.0 DISCUSSION

Fibroids are a significant public health issue and there is a lot of interest in the UAE from provider and patient groups in what is, compared to the alternatives available, a minimally invasive procedure. UAE widens the treatment options for suitable patients who wish to avoid major surgery or are poor surgical risks. The numbers of procedures carried out world-wide are unknown but, the published literature indicates that the expertise is concentrated in a relatively small number of centres in the USA, England and

France. A survey in 2000[4] reported that 8,500 had been performed in the USA. It is estimated that 2,050 procedures have been carried out in the UK to date, mostly in one centre in London and the South East (Table 1).

In the short- term there is evidence to show that UAE reduces the size and volume of fibroids in most patients. Greater reductions are associated with larger fibroids and those with increased vascularity. The reductions in volume achieved have been found not to correspond with improvements in symptoms. Short-term improvements in the symptoms (most frequently menorrhagia) in most patients are reported. The extent of these improvements could not be determined from the papers reviewed. Two papers from series of less than 100 patients reported complete resolution of symptoms in 90% to 100%,[60] of patients. 'Marked improvements' (as distinct from 'moderate' or 'slight' were reported as occurring in 34% to 58% of patients in the largest series. These results cannot be compared with those based on the other large series of patients. Differences in the amount of improvement[25,73] or improvement or stabilisation were not reported, and no uniform or consistent criteria to evaluate results or uniform definitions that would allow comparisons to be made was found.

In respect of safety, there was wide variation in the rate (5% to 73%). Almost certainly these proportions will be affected by differences in the size of the case series and in how complications are defined. The rates in the larger studies, (with follow up at six months), of between 6%-13% are within the range of the overall complication rate 10.5% reported in the one study that used standardised criteria for complications.

Pain and post-embolisation syndrome are not uncommon. A number of other events – some life-threatening - have been reported. Based on the available data, rates of conversion to hysterectomy were between 1.3%[57] and 11.5%. Late passage of fibroid tissue is reported as occurring more than a year following UAE[25,74]. The impact on fertility appears to be small but there are uncertainties about the mechanism by which UAE ovarian dysfunction occurs. Permanent ovarian dysfunction is reported in a small number of cases, and this possibility raises issues for women who desire future pregnancy.

The implications of morphologic changes found in excised post-UAE tissue[21,50,]are uncertain.

The optimum protocol is still being developed. Operator confidence and competence are relevant safety issues and the sharing of care between the two specialties raises questions about the optimum care of patients in the immediate and delayed post-UAE period.

The limitations of the available evidence are that there is only one small RCT[45] (n = 38 vs n=19) comparing UAE with hysterectomy and this is of moderate quality. The comparative results remain reasonably robust, although the small size of the trial means that the results are not precise. The study provides weak evidence that the rate of any complication within 30 days of the procedure was higher in the UAE group (73%) than in the hysterectomy group (45%), but the crossover confounded comparison of the rates between the groups. The design of the comparative studies[52,54] did not permit valid comparisons to be made between patients who had UAE and those who had myomectomy. Predominantly therefore, the evidence is contained in uncontrolled case series of varying size. All the patients are a selected to highly selected group. How representative they are of the relevant UK patient population is uncertain. The results reported will be affected by selection bias and patients lost to follow up. Other limitations are variations in reporting, and the use of unvalidated outcome measures that make it difficult to assess the clinical importance of the improvements reported. As these are linked to patient satisfaction meaningful comparisons between studies cannot be made. The evidence reviewed permits only tentative conclusions about the safety and efficacy of UAE to be drawn.

7.0 CONCLUSION

There is evidence of short-term improvements in the symptoms in between 60% and $\geq$90% of patients treated with the UAE, particularly for those presenting with symptoms of menorrhagia. The extent and durability of any improvement is unclear.

In respect of safety, UAE results in a small number of serious complications in the short term[36,73,74]. No reliable data comparing complication rates with other interventions was available in the papers reviewed.

The important factors that distinguish UAE from other treatment options, (subject to clinical suitability for treatment), are patient choice and fertility.

Longer term, larger randomised controlled trials comparing UAE with other treatments for managing the symptoms of fibroids in the UK population are required.

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APPENDICES

Systematic review of the efficacy and safety of uterine artery embolisation in the treatment of fibroids

Appendix 1

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

REVIEW BODY FOR INTERVENTIONAL PROCEDURES

Uterine Artery Embolisation for Fibroids

Scope
12th August 2003

Objective
To systematically review the evidence for efficacy and safety of Uterine Artery Embolisation (UAE) for fibroids.

Intervention
Uterine artery embolisation is one of the newer minimal access procedures for fibroids. Others include laparoscopic and hysteroscopic myomectomy. The aim of minimal access procedures is to reduce the recovery time and operative risks compared with conventional techniques.

UAE involves injecting embolising material to block the blood supply to the fibroids. A catheter inserted into a femoral artery under local anaesthetic is fed into uterine arteries under x-ray control. Both uterine arteries are blocked with these particles. The normal muscle of the uterus takes a new blood supply from other vessels that supply it. However, usually, the fibroids do not revascularise. Consequently, the fibroids shrink, and evidence to date suggests there is no adverse effect on the normal muscle of the uterus. Pain can be severe for up to 8 hours post-procedure and opiate analgesia is usually required. Patients are usually in hospital for 24-36 hours because of the pain relief they require, and are advised to rest for 1-2 weeks. Fibroid embolisations are performed by an interventional radiologist.

Background
Uterine fibroids, also known as uterine leiomyomas or uterine myomas, are benign tumours of the uterus. Fibroids are the commonest gynaecological problem of women in the UK and are one of the most frequent reason for a hysterectomy. Symptoms include pain, pelvic pressure, and excessive bleeding. In addition fibroids may be associated with sub-fertility.

UAE is likely to be seen as an alternative to hysterectomy or myomectomy, and is particularly attractive to women wanting to avoid surgery. It probably necessitates a shorter hospital stay and recovery time, and results in fewer major complications. Most imaging studies focus on volume reduction. It is known that there is a small recurrence rate or that some fibroids fail to degenerate.

Sepsis following necrosis of the fibroid is the most serious and most common adverse event. If severe it can lead to death (two cases in the worldwide literature) and a variable incidence of unwanted and often difficult hysterectomy (1:50 – 1:200). However, current observational trials have demonstrated a very high efficacy of the procedure with a morbidity and mortality rate lower than surgery. Many thousands of women have had the procedure, the majority with apparent success. Although a total of four women are known to have died after UAE (two from septicaemia and two from pulmonary emboli), the alternative surgical procedures of hysterectomy and myomectomy are also associated with a small but significant mortality rate and significant morbidity. Advice in the UK is not to perform UAE for fibroids in patients with a history of pelvic infection[1].

There are also issues about the place of UAE and its safety in large fibroids, especially in relation to infertility. Infertility following the procedure due to premature ovarian failure or intra-cavity adhesions is poorly quantified. Conversely, there are multiple papers in the literature describing successful pregnancies after UAE for a variety of pathologies, but only limited clinical data are available on this. Some specialists recommend that patients desiring future pregnancies explore other treatment possibilities such as myomectomy before considering UAE.

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[1] Royal College of Radiologists and Royal College of Obstetricians and Gynaecologists (2000) *Clinical Recommendations on the Use of Uterine Artery Embolisation in the Management of Fibroids: Report of a joint working party* London: Royal College of Obstetricians and Gynaecologists.

Population
Fibroids occur in women from 15-90 years of age, and are more common in Afro-Caribbean women.

Current forms of management for patients who might be considered for UAE for fibroids
1. Traditionally, women were offered hysterectomy or myomectomy.

2. There is no medical treatment for uterine fibroids. GnRH agonists can be administered but this is a temporary treatment, normally used to shrink the fibroids prior to surgery, and generally cannot be used for more than six months.

Efficacy issues
The efficacy of UAE for fibroids will be assessed using subjective and objective measures of outcome including reduced fibroid bulk, symptom relief (menorrhagia, pressure and pain symptoms), pregnancy rates, quality of life and patient satisfaction. It is important to note that there may be different end points depending on whether UAE for fibroids is an alternative to myomectomy or hysterectomy.

Safety issues
Potential adverse events include: amenorrhoea in younger women, uterine infection, premature ovarian failure, fibroid expulsion (no sequelae), persistent discharge (up to three months), failure of a technically successful procedure leading to hysterectomy, sepsis following necrosis of the fibroid, and infertility. Concerns exist about radiologists who perform this procedure without first securing the advice and support of a gynaecologist and about 'lone' radiologists who only invite gynaecological assistance when significant complications have already occurred.

Data gathering strategy
Evidence on efficacy and safety will be identified using a number of strategies: electronic searches, searching of grey literature (such as conference proceedings), population databases, experts' opinions and reference lists of identified studies. For evidence on patient satisfaction outcomes the strategy employed will utilise searches of electronic databases, grey literature and referenced lists of identified studies. Experts' opinions may also be canvassed where relevant.

Analysis strategy
Evidence will be considered if possible in order of design quality, the hierarchy of designs depending on the parameter being considered. Data will be abstracted independently, by two assessors using standard abstraction forms, and tabulated. Where possible, results will be summarised using standard statistical methods.

Other considerations
Other considerations which may have to be taken into account during this review relate to the training and experience of radiologists who wish to undertake this procedure and the division of patient management responsibilities between radiologists and gynaecologists.

APPENDIX 2

LITERATURE SEARCH

DATABASES and SEARCH TERMS

Electronic Bibliographic Databases Searched

1. BIOSIS
2. Cinahl
3. Cochrane Library (CENTRAL, DARE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, NHS EED, HTA)
4. CRD Databases (DARE, NHS EED, HTA)
5. Current Controlled Trials
6. Dissertation Abstracts
7. Embase
8. HTA Projects and Publications Database
9. Index to Thesis
10. ISI Conference Proceeding
11. Medical Research Council (MRC) Clinical Trials Register
12. Medline
13. National Research Register
14. PreMedline
15. Research Findings Register (ReFeR)
16. Tripdatabase
17. Web of Science (Science Citation Index and Social Science Citation Index)

Search Strategies Used in the Major Electronic Bibliographic Databases

BIOSIS
1985-2003
SilverPlatter WebSPIRS
Search undertaken October 2003

#1 uter* fibroid*
#2 myofibro*
#3 myom*
#4 leiomyom*
#5 benign tumo?r*
#6 benign near5 tumo?r*
#7 uter* neoplasm*
#8 uter* cancer*
#9 uter* tumo?r*
#10 uter* growth*
#11 or/ #1 – #10
#12 uter* arter* emboli?ation*
#13 emboli?ation*
#14 uae
#15 embolotherap*
#16 or/ #12 - #15
#17 #11 and #16

Cinahl
1966-2003
Ovid
Search undertaken October 2003

#1 uter$ fibro$.tw.
#2 myofibro$.tw.
#3 myom$.tw.
#4 leiomyoma/
#5 leiomyom$.tw.
#6 benign adj10 tumo?r$).tw.
#7 uterine Neoplasms/
#8 (uter$ adj10 neoplasm$).tw.
#9 uter$ cancer$.tw.
#10 uter$ growth$.tw.
#11 uter$ tumo?r$.tw.
#12 or/ #1 - #11
#13 Embolization, Therapeutic/
#14 emboli?ation$.tw.
#15 uter$ arter$ emboli?ation$.tw.
#16 uae.tw.
#17 embolotherap$.tw.
#18 or/ #13 - #17
#19 #12 and #18

Cochrane Library
The Cochrane Library, Update Software (Online version)
Search undertaken October 2003

#1	(uter* next fibroid*)
#2	MYOFIBROMATOSIS single term (MeSH)
#3	myofibro*
#4	MYOMA explode tree 1 (MeSH)
#5	myom*
#6	LEIOMYOM explode tree 1 (MeSH)
#7	leiomyom*
#8	(benign next tumor*)
#9	(benign next tumour*)
#10	UTERINE NEOPLASMS explode tree 1 (MeSH)
#11	(uter* next neoplasm*)
#12	(uter* next cancer*)
#13	(uter* next growth*)
#14	(uter* next tumor*)
#15	(uter* next tumour*)
#16	or/ #1 - #15
#17	(uter* next arter* next embolization*)
#18	(uter* next arter* next embolisation*)
#19	EMBOLIZATION THERAPEUTIC explode tree 1 (MeSH)
#20	embolisation*
#21	embolization*
#22	uae
#23	embolotherap*
#24	or/ #17 – #23
#25	#16 and #24

CRD Databases (NHS DARE, EED, HTA)

CRD website. Complete databases
Search undertaken October 2003

#1	uterine artery embolisation
#2	uterine artery embolization
#3	uae
#4	embolotherapy
#5	or/ #1 - #4

Embase
1980-2003
SilverPlatter WebSPIRS
Search undertaken October 2003

#1	explode 'uterus-myoma' / all subheadings
#2	explode 'myoma-' / all subheadings
#3	myom*
#4	explode 'myofibrosis-' / all subheadings
#5	myofibro*
#6	explode 'leiomyoma-' / all subheadings
#7	leiomyom*
#8	uter* near10 fibro*
#9	uter* near5 benign near3 tumo?r*
#10	explode 'uterus-cancer' / all subheadings
#11	uter* near10 cancer*
#12	uter* near5 neoplasm*
#13	explode 'uterus-growth' / all subheadings
#14	uter* near5 growth*
#15	explode 'uterus-tumor' / all subheadings
#16	uter* near5 tumo?r*
#17	or/ #1 – #16
#18	explode 'uterine-artery-embolization' / all subheadings
#19	uter* near5 arter* near5 emboli?ation*
#20	uae
#21	explode 'artificial-embolism' / all subheadings
#22	artificial embolism*
#23	emboli?ation*
#24	embolotherap*
#25	or/#18- #24
#26	#17 and #25

Medline
1966-2003
Ovid
Search undertaken October 2003

#1	(uter$ adj10 fibro$).tw.
#2	myofibro$.tw.
#3	exp Myoma/
#4	myom$.tw.
#5	exp Leiomyoma/
#6	leiomyom$.tw.
#7	(uter$ adj5 benign adj3 tumo?r$).tw.
#8	Uterine Neoplasms/
#9	(uter$ adj5 neoplasm$).tw.
#10	(uter$ adj5 cancer$).tw.
#11	(uter$ adj5 growth$).tw.
#12	or/ #1 - #11
#13	EMBOLIZATION, THERAPEUTIC/
#14	emboli?ation$.tw.
#15	(uter$ adj5 arter$ adj5 emboli?ation$).tw.)
#16	uae.tw.
#17	embolotherap$.tw.
#18	or/ #13 - #17
#19	#12 and #18

Medline In Process

October 3rd 2003
Ovid

#1 uter$ fibroid$.tw.
#2 myofibro$.tw.
#3 myom$.tw.
#4 leiomyom$.tw.
#5 benign tumo?r$.tw.
#6 uter$ neoplasm$.tw.
#7 uter$ cancer$.tw.
#8 uter$ growth$.tw.
#9 uter$ tumo?r$.tw
#10 or/ #1 - #9
#11 uter$ arter$ emboli?ation$.tw.
#12 emboli?ation$.tw.
#13 uae.tw.
#14 embolotherap$.tw.
#15 or/ #11 - #14
#16 #10 and #15

Web of Science

1981-2003
MIMAS
Search undertaken October 2003

#1 uter* arter* embolization*
#2 uter* arter* embolisation*
#3 uae
#4 embolotherap*
#5 or/ #1 – #4
#6 uter* fibroid*
#7 myofibro*
#8 myom*
#9 leiomyom*
#10 benign tumor*
#11 benign tumour*
#12 uter* neoplasm*
#13 uter* growth*
#14 uter* cancer*
#15 uter* tumor*
#16 uter* tumour*
#17 or/ #6 – #16
#18 #5 and #17

APPENDIX 3

List of Non-English Language publications
No translations obtained

Alonso AM, Marret H, Herbreteau D, Perrotin F, Bouquin R, Body G. [Prospective clinical and sonographic assessment of uterine artery embolization as the treatment of symptomatic uterine leiomyomata]. [French]. Gynecologie, Obstetrique & Fertilite 2003;**31**:117-22.

Ankum WM,.Reekers JA. [Embolization of uterine artery: a new treatment for uterine myomas]. [Review] [22 refs] [Dutch]. Nederlands Tijdschrift voor Geneeskunde 2001;**145**:765-9.

Bouquet DJ, Levardon M, Sitbon D. Embolization of Fibroids L'Embolisation des Fibromes. Reproduction Humaine et Hormones 1996;**9**:533-7.

Bouret JM. [Role of embolization in myomatous pathology]. [Review] [22 refs] [French]. Journal de Gynecologie, Obstetrique et Biologie de la Reproduction 1999;**28**:753-60.

Bouret JM. Recommendations for clinical practice. Management of uterine fibroma: The role of embolization in myomatous pathology. Journal de Gynecologie Obstetrique et Biologie de la Reproduction 1999;**28**:753-60.

Chen C, Lu J, Liu P, Yu L, Ma B, Liu P. Clinical analysis of 42 cases uterine myoma by uterine arterial embolization. [Chinese]. Chung-Hua Fu Chan Ko Tsa Chih [Chinese Journal of Obstetrics & Gynecology] 2002;**37**:8-11.

Cohen J. [Fibroma: surgical myomectomy or embolization or GnRH analogs? Intramural and sub-serous fibroma: start with medical treatment!]. [French]. Gynecologie, Obstetrique & Fertilite 2001;**29**:64-6.

Gaetje R, Zangos S, Vogl T, Kaufmann M. Infection after embolisation of uterine leiomyomata requiring hysterectomy. Geburtshilfe und Frauenheilkunde 2003;**63**:156-9.

Golfieri R, Muzzi C, De Iaco P, Maffei M, Giampalma E, Amore B et al. [The percutaneous treatment of uterine fibromas by means of transcatheter arterial embolization]. [Italian]. Radiologia Medica 2000;**100**:48-55.

Golzarian J, Murgo S, Laureys M, Tannouri F, Struyven J. [Uterine fibroids embolization: a review]. [Review] [31 refs] [French]. Jbr-Btr: Organe de la Societe Royale Belge de Radiologie 2002;**85**:7-13.

Henry F. [Uterine artery embolization for symptomatic uterine fibromas. Informed consent of the patient]. [French]. Journal de Radiologie 2001;**82**:111-5.

Honda I, Sato T, Adachi H, Kobayashi Y, Shimada K, Watanabe H et al. Uterine artery embolization for leiomyoma: complications and effects on fertility. [Japanese]. Nippon Igaku Hoshasen Gakkai Zasshi - Nippon Acta Radiologica 2003;**63**:294-302.

Kroncke TJ, Gauruder-Burmester A, Hamm B. [Uterine fibroid embolization - a new therapeutic option for symptomatic leiomyomata of the uterus]. [Review] [57 refs] [German]. ROFO-Fortschritte auf dem Gebiet der Rontgenstrahlen und der Bildgebenden V 2002;**174**:1227-35.

Lohle PN, Lampmann LE, Boekkooi PF, Vervest HA, Pieters JJ. [Embolization as treatment for symptomatic uterus myomata]. [Dutch]. Nederlands Tijdschrift voor Geneeskunde 2001;**145**:791-4.

Maltau JM, Kumar S, Singh K, Sildnes T, Busch E. [Percutaneous embolization of uterine arteries in uterine myoma]. [Review] [31 refs] [Norwegian]. Tidsskrift for Den Norske Laegeforening 2003;**123**:614-6.

Murgo S, Simon P, Golzarian J. [Embolization of uterine fibroids]. [Review] [74 refs] [French]. Revue Medicale de Bruxelles 2002;**23**:435-42.

Pelage JP, Le Dref O, Jacob D, Soyer P, Rossignol M, Truc JB et al. [Uterine embolization]. [French]. Journal de Radiologie 2000;**81**:1873-4.

Pelage JP. Uterine fibroid embolization: present and future? Journal de Radiologie 2000;**81**:483-4.

Pietura R, Kotarski J, Janczarek M, Jaskowiak R, Czekierdowski A, Szczerbo-Trojanowska M. [Submucosal symptomatic leiomyoma treated with transcatheter uterine artery embolisation--case report]. [Polish]. Ginekologia Polska 2003;**74**:69-72.

Ravina JH, Aymard A, Ciraru VN, Bouret JM, Houdart E, Ledref O et al. Selective arterial embolization for hemorrhagic uterine leiomyomas. Presse Medicale 1998;**27**:299-303.

Ravina JH, Aymard A, Ciraru-Vigneron N, Ledreff O, Merland JJ. [Arterial embolization of uterine myoma: results apropos of 286 cases]. [French]. Journal de Gynecologie, Obstetrique et Biologie de la Reproduction 2000;**29**:272-5.

Ravina JH. Arterial embolization in the treatment of uterine myomas. Reproduction Humaine et Hormones 2001;**14**:76-82.

Ravina JH. [Fibroma: surgical myomectomy or embolization or GnRH analogs? Embolization of uterine fibroma: a new treatment]. [French]. Gynecologie, Obstetrique & Fertilite 2001;**29**:66-7.

Salerno S,.Belli AM. [Percutaneous treatment of uterine fibroleiomyomas: analysis of complications and quality of life after embolization]. [Italian]. Radiologia Medica 2001;**101**:360-4.

Siggelkow W, Gunther R, Neulen J, Rath W. Uterine artery embolization for the treatment of uterine fibroids. Geburtshilfe und Frauenheilkunde 2002;**62**:131-138138.

Simonetti G, Romanini C, Pocek M, Piccione E, Guazzaroni M, Zupi E et al. [Embolization of the uterine artery in the treatment of uterine myoma]. [Italian]. Radiologia Medica 2001;**101**:157-64.

Trastour CB. [Pregnancy after embolization of symptomatic leiomyomata]. Gynecologie, Obstetrique & Fertilite 2003;**31**:243-5.

Vogl TJ, Jacobi V, Gatje R, Siebzehnrubl E, Zangos S. Embolization of symptomatic myomas (UAE): Technique, indication and results. Rofo-Fortschritte Auf dem Gebiet der Rontgenstrahlen und der Bildgebenden Verfahren 2003;**175**:1032-41.

APPENDIX 4

Review of the Safety and Efficacy of Uterine Artery Embolization

Critera for inclusion based on the predicted quality of study design

Distinguished:		Description/Justification
	Primary	
√√√√√	Randomised Controlled Trials	Randomised allocation of patients to UAE treatment group and other treatment group. Dispassionate observance of outcomes.
√√√√	Comparative studies	Compare patients in intervention with patients (matched) receiving different treatment
√√√√	Multi-centre prospective single arm clinical treatment trial	Systematic prospective cases series of patients treated in >one clinical setting – potential to reduce bias from concentration of expertise or facilities associated with single centre trials.
√√√	Prospective longitudinal study	Prospective case series followed over a specified time – potentially longer term outcomes
√√	Before and After	Express reporting of measures pre and post procedure potentially higher than retrospective or unqualified prospective
√	Observational clinical study	Prospective or retrospective case series
√	Prospective case series	Higher than retrospective in reducing potential bias from differences between patients or procedures
√	Retrospective	Low - most opportunity for bias

APPENDIX 5.1

CASE REPORT summaries – published 2000 or later,
(Other than UK - see Table 1.3).

Author	Country	Age	Reported outcome
Ambekar	USA	52	Aberrant uterine artery as a cause of UAE treatment failure
Andrews	USA	34	Results non-selective pelvic arteriogram to identify and treat collateral arteries
Bouffard	USA	40	Resolution of symptoms
Common	Canada	49	Near fatality due to unrecognised underlying leiomyosarcoma.
DeBlok	The Netherlands	42	Fatality from septic shock
De Laco	Italy	54	Uterine wall defect 14 months post UAE
Felemban	Canada	43	Expulsion of myomas vaginally 21-35 days post UAE; symptomatic improvement
Garcia	USA	54, 35	Two x cases. symptom improvement
Godfrey	USA	45	Diffuse uterine necrosis - Laparotomy, total hysterectomy and left salpingooophorectomy
Goldberg	USA	42	Complicated pregnancy and subsequent hysterectomy
Hagspiel	USA	37: 51	Pilot to demonstrate feasibility of perfusion-weighted EST magnetic resonance imaging.
Hameed	USA	53	Diagnosed post UAE squamous mataplasia; progestational therapy; hysterectomy
Has	Turkey	36	15 days post UAE. Surgical evacuation of pregnancy. Potentially, future fertility preserved; 11 months amenorrhoea observed
Huang	Taiwan	41	Incomplete vaginal expulsion of pyoadenomyoma with sepsis and focal bladder necrosis
Kido	Japan	31	Symptomatic improvement of diffuse leiomyomatosis
Kovacs	USA	35	Post UAE laparotomy and myomectomy; transient ovarian failure: successful conception
Kroencke	Germany	48	Improvement and shrinkage of fibroids : uneventful expulsion of infarcted tissue 7 months post-UAE
Onder	Turkey	22	Uterine fibroid with menorrhagia and pelvic pressure managed successfully with UAE
Payne	USA	39; 47	Serious complications post UAE– delayed detection of sarcoma : emergency hysterectomy
Pollard	USA	40	Large cervical myoma prolapse; abdominal hysterectomy
Shashoua	USA	44	Ischemic uterine rupture 3 months post UAE: hysterectomy
Stringer	USA	45	Ovarian failure 4 weeks post UAE
Stringer	USA	53	Rare myoma: Laparoscopic myometomy post UAE
Sultana	USA	43	Extrusion of degenerating leiomyoma into bladder: hysterectomy and partial cystectomy

Vitale	USA	37; 49	Two-cases short-term symptom improvements; Sonographic and colour-flow Doppler findings pre and post and 3 months post-UFE
Yeagley	USA	38	Labial necrosis as possible complication of UAE

APPENDIX 5.2

References to Case Reports 2000 (Appendix 5.1) and later (except UK – see Table 1.3)

Ambekar A,.Vogelzang RL. Aberrant uterine artery as a cause of uterine artery embolization treatment failure. International Journal of Gynecology and Obstetrics 2001;**74**:59-60.

Andrews RT, Bromley PJ, Pfister ME. Successful embolization of collaterals from the ovarian artery during uterine artery embolization for fibroids: A case report. Journal of Vascular and Interventional Radiology 2000;**11**:607-10.

Bouffard J, Swett D, Cardona B, Moger A. The use of sonography in uterine artery embolization. Journal of Diagnostic Medical Sonograph 2003;**19**(1):39-42.

Common AA, Mocarski EJ, Kolin A, Pron G, Soucie J. Therapeutic failure of uterine fibroid embolization caused by underlying leiomyosarcoma. Journal of Vascular & Interventional Radiology 2001;**12**:1449-52.

de Blok S.de Vries. Fatal sepsis after uterine artery embolization with microspheres. Journal of Vascular & Interventional Radiology 2003;**14**:779-83.

De Iaco PA, Muzzupapa G, Golfieri R, Ceccarini M, Roset B, Baroncini S. A uterine wall defect after uterine artery embolization for symptomatic myomas. Fertility & Sterility 2002;**77**:176-8.

Felemban A, Stein L, Tulandi T. Uterine restoration after repeated expulsion of myomas after uterine artery embolization. Journal of the American Association of Gynecologic Laparoscopists 2001;**8**:442-4.

Garcia MJ, Gheyi VK, Uppot RN, Nowakowski FS, Storm ES. Uterine fibroids: primary treatment with therapeutic embolization. Delaware Medical Journal 2000;**72**:397-401.

Godfrey CD,.Zbella EA. Uterine necrosis after uterine artery embolization for leiomyoma.[comment]. Obstetrics & Gynecology 2001;**98**:950-2.

Goldberg J, Pereira L, Berghella V. Pregnancy after uterine artery embolization. [Review] [18 refs]. Obstetrics & Gynecology 2002;**100**:869-72.

Hagspiel K D, Matsumoto AH, Berr SS. Uterine Fibroid Embolization: Assessment of Treatment Response using perfusion-weighted extraslice spin tagging (EST) magnetic resonance imaging. Journal of Magnetic Resonance Imaging 2001;**13**:292-986

Hameed M, Heller DS, Murphy G. Squamous metaplasia of endometrium after uterine artery embolization for symptomatic leiomyomata. Journal of the American Association of Gynecologic Laparoscopists 2002;**9**:70-2.

Has R, Balci NC, Ibrahimoglu L, Rozanes I, Topuz S. Uterine artery embolization in a 10-week cervical pregnancy with coexisting fibroids. International Journal of Gynecology & Obstetrics 2001;**72**:253-8.

Huang LY, Cheng YF, Huang CC, Chang SY, Kung FT. Incomplete vaginal expulsion of pyoadenomyoma with sepsis and focal bladder necrosis after uterine artery embolization for symptomatic adenomyosis: Case report. Human Reproduction 2003;**18**:167-71.

Kido A, Monma C, Togashi K, Ueda H, Itoh K, Fujii S et al. Uterine arterial embolization for the treatment of diffuse leiomyomatosis. Journal of Vascular and Interventional Radiology 2003;**14**:643-7.

Kovacs P, Stangel JJ, Santoro NF, Lieman H. Successful pregnancy after transient ovarian failure following treatment of symptomatic leiomyomata. Fertility & Sterility 2002;**77**:1292-5.

Kroencke TJ, Gauruder-Burmester A, Enzweiler CNH, Taupitz M, Hamm B. Disintegration and stepwise expulsion of a large uterine leiomyoma with restoration of the uterine architecture after successful uterine fibroid embolization: Case report. Human Reproduction 2003;**18**:863-5.

Onder C, Seyma H, Kaya S. Uterine artery embolization. Indian Journal of Radiology and Imaging 2002;67-9.

Payne JF,.Haney AF. Serious complications of uterine artery embolization for conservative treatment of fibroids. Fertility and Sterility 2003;**79**:128-31.

Pollard RR,.Goldberg JM. Prolapsed cervical myoma after uterine artery embolization. A case report. J Reprod.Med 2001;**46**:499-500.

Shashoua AR, Stringer NH, Pearlman JB, Behmaram B, Stringer EA. Ischemic uterine rupture and hysterectomy 3 months after uterine artery embolization. Journal of the American Association of Gynecologic Laparoscopists 2002;**9**:217-20.

Stringer NH, Grant T, Park J, Oldham L. Ovarian failure after uterine artery embolization for treatment of myomas. Journal of the American Association of Gynecologic Laparoscopists 2000;**7**:395-400.

Stringer NH, DeWhite A, Park J, Ghodsizadeh A, Edwards M, Kumari NV et al. Laparoscopic myomectomy after failure of uterine artery embolization. Journal of the American Association of Gynecologic Laparoscopists 2001;**8**:583-6.

Sultana CJ, Goldberg J, Aizenman L, Chon JK. Vesicouterine fistula after uterine artery embolization: a case report. American Journal of Obstetrics & Gynecology 2002;**187**:1726-7.

Vitale J,.Zambuto D. Uterine fibroid embolization: sonographic findings pre- and postembolization. J diagn.med sonography 2001;**17**:167-71.

Yeagley TJ, Goldberg J, Klein TA, Bonn J. Labial necrosis after uterine artery embolization for leiomyomata. Obstetrics and Gynecology 2002;**100**:881-2.

APPENDIX 6

Quality assessment tool for randomised controlled trials

Criteria	Yes	No	Unclear
1. Was the assignment to the treatment groups really random?			
2. Was the treatment allocation concealed?			
3. Were the groups similar at baseline in terms of prognostic factors?			
4. Were the eligibility criteria specified?			
5. Were the groups treated in the same way apart from the intervention received?			
6. Was the outcome assessor blinded to the treatment allocation?			
7. Was the care provider blinded?			
8. Were the patients blinded?			
9. Were the point estimates and measures of variability presented for the primary outcome measures?			
10. Was the withdrawal/drop-out rate likely to cause bias?			
11. Did the analyses include an intention-to-treat analysis?			

APPENDIX 7

Quality assessment for non-randomised case series **Criteria**	**Yes**	**No**	**Unclear**
1. (a) Where participants selected from a relevant patient population? (b) Were they representative?			
2. Were the inclusion/exclusion criteria of patients in the study clearly described?			
3. Were participants entering the study at a similar point in their disease progression?			
4. Was selection of patients consecutive?			
5. Were all important prognostic factors identified?			
6. Was data collection undertaken prospectively?			
7. Was the recruitment period clearly stated?			
8. Was the intervention that which is being considered in the review?			
9. Was the Operator's experience described?			
10. Was the place, and facilities where the patients were treated described?			
11. Were objective (valid and reliable) outcome measures used?			
12. What clinical outcomes were reported?			
13. What was the period of follow-up?			
14. Was information provided on all patients in the series initially?			
15. Were participants lost to follow-up likely to introduce bias?			
16. Were the main findings clearly described?			

APPENDIX 8

Separate summaries of 35 papers reviewed
(alphabetic order of first author)

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Ahmed 2002[75] Kuwait One centre **Date** October 1997 March 2001 **Funding**: None declared	**case series** prospective **Patients**: 32 **Mean age**: 34 (26-45) Refused surgical intervention; Poor candidates for myomectomy. Did not desire future fertility; or option other than UAE hysterectomy only. 4/32 previous myomectomy 7/32 previous cesarean sections 1/32 left ovarian resection **Pre-UAE –** Ultrasound Clinical and biochemical tests **Post-UAE** Follow up 1 and 6 weeks, 3 and 6 months	**Included:** Patients referred following gynaecological examination. and diagnosis of symptomatic fibroids pre or peri-menopausal and no desire for future pregnancy Excessive menstrual bleeding; pelvic pain or press or both. 9/32 anaemia 30 normal baseline ovarian function. 2 peri-menopausal	32 bilateral Same interventional radiologist **Embolizing materials** 500-700 *u*m dia Polyvinyl alcohol foam particles **Endpoint** Cessation of antegrade blood flow in uterine artery **Procedure time** Mean 90 (range, 45-120) minutes	Reduction in fibroid and uterine volume Effect on ovarian function	**Efficacy** At least 30% reduction in fibroid size. **Safety** Fertility 30/32 patients resumed normal menses 2-3 months post procedure. FSH level 3 months 6.99 IU/L ± 1.67 6 months 6.7 IU/L ± 1.18 2/32 (peri-menopausal at baseline) irregular menses. FSH level Pre;UAE 30 IU/L and 22 IU/L Post UAE 3 months 48 IU/L and 40 IU/L 6 months 26 IU/L and 27 IU/L Normal menses resumed 8 and 10 months post UAE respectively. Evidence of transient ovarian dysfunction in peri-menopausal patients.

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Banovac 2002[62] USA Single-centre **Date** Not reported **Funding**: Co-author Research grants from Biosphere Medical	**Before and After UAE** Retrospective notes review of MR images. **Patients**: 23 **Mean age**: 42 (28-52) 61 fibroids in total – 35/61 intramural 15/61 serosal 11/61 broad-based submucosal or pedunculated submucosal or pedunculated serosal. **Pre-UAE** MR Imaging **Post-UAE** Review of pre and post MRI images: 3 months by two experienced IR (other than operating IR)	**Included:** Pre UAE MR images undertaken at operating institution; Symptomatic fibroids - bleeding or pelvic pain.	23 bilateral Experienced interventional radiologist (IR) **Embolizing material**: 21/23 Tris-acryl gelatin microspheres:500-700 *u*m or 700-900 *u*m dia. or combinations. 1/23 300-500 *u*m dia. or combinations 1/23 700-900 and combination of 900-1200 *u*m dia. Variation : operator choice **Endpoint** Slow in flow in uterine arteries sufficient for contrast material to remain visible in the main ascending uterine artery for at least 5 cardiac beats but cleared in several seconds. Angiographic endpoint central vasculature of leiomyomata occluded proximal portions of feeding vessels remaining patent without significant forward flow 'pruned branch appearance'	Median reduction in: fibroid volume; dominant fibroid volume; uterine volume No clinical outcomes	**Efficacy** Median volume reduction at 3 months % Change 95% CI All Fibroids (61*) 52% (41%,63%) Dominant (21*/23) 52% (40%,69%) Uterine 32% (23%,43%) 2*/61 fibroids not found 1/61 fibroid no reduction **Safety** No complications reported

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Bapuraj 2002[76] India Single-centre **Date** March 2000- March 2001 **Funding**: None declared	**Case series** **Patients**: 11 **Mean age**: 31.6 (22-50) **Pre-UAE –** Ultrasound one day before UAE **Post-UAE** Clinical follow up 15 days Ultrasound 2 and 6 months	**Included:** Diagnosis of fibroids confirmed by ultrasound and examination by experienced gynaecologist 11/11 Menorrhagia 7/11 pelvic pain 6/11 bulk symptoms 5/11 chronic anaemia 11/11 strong desire to avoid surgery 11/11 hypervascular uterus No other gynaecologic or medical problems; No contraindications to arteriography;	Inpatient 11/11 bilateral Experienced interventional radiologist **Embolizing material**: 350-500 *u*m polyvinyl alcohol particles gelatin sponge slurry **End-point**: Complete cessation of flow or reflux of contrast material into anterior division of internal iliac artery	Diagnostic Mean reduction in: dominant fibroid volume; uterine volume. Clinical Pelage[57] 5-point scale: 1 Complete resolution 2 Marked improvement 3 Slight improvement 4 No improvement 5 Worsening of symptoms	**Efficacy** Mean reduction volume: 2 months % / 6 months* % Dominant fibroid 38.76 / 56.34 Uterine 27.48 / 45.34 **Safety*** *6 patients* 1/11 severe pain 1/11 post-embolization syndrome 6/11 hospital stay >24 hours Mean hospital stay 1.9 days Clinical 10/11 Improvement 1-3 Pelage scale 1/11 No improvement : Menorhaggia

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Broder 2002[52] USA Single-centre **Date** December 2000 **Funding**: In part by UCLA Building Interdisciplinary Research Careers in Women's Health Program	**Comparative case series** Retrospective notes review **Patients**: 59/97 (UAE/all) July 1996-August 1997 Ethnicity **51 patients* White 23 Non-white 28 **Mean age**: 44 (31-56) **Post UAE** Notes review and Telephone survey mean follow up 46 (41-59) months	**Included** Multiple symptoms Most had previous surgical procedures for fibroids** *** performed preoperatively by clinical protocol in many UAE patients at this institutiton – practice discontinued*	Inpatient Not described	**Changes in symptoms**: Symptom scale 1-5 Clinical improvement scale 1-7 **Patient satisfaction** 1-4 (very satisfied to very dissatisfied) **Criteria for Failure** 1. Need for additional invasive treatment for myomas; 2. No improvement or worsening in overall symptom score; 3. Self-rated dissatisfied or very dissatisfied. **Any one = clinical failure**	**Long-term efficacy** **51 patients* 29% (n=15) further invasive therapy 6 hysterectomies 8 myomectomies 1 repeat UAE 20/51 'clinical failure' rate 39% 31/61 'at least somewhat satisfied' 61%

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Burn 2000[18] UK Single-centre **Date** Not reported **Funding**: None declared	**Before and After** **Patients**: 18 **Mean age**: 39 (28-53) 32 fibroids in total - Volume mean 340 cm^3 (15-1383 cm^3) 16 larger (144-1383 cm^3) 16 smaller (9-108 cm^3) **Pre-UAE –** MRI one day before UAE **Post-UAE** MRI images: 2 and 6 months reviewed by two experienced IRs (other than operating IR)	**Included:** Consecutive patients with diagnosis of fibroids confirmed by ultrasound and gynaecological examination Menorrhagia or abdominal distension or discomfort; Otherwise candidates for surgical resection	16/18 bilateral 2/18 unilateral Experienced interventional radiologist	Mean reduction in: fibroid volume; No clinical outcomes	**Pre-UAE MRI** high signal intensity T1-weighted images predictive of poor response; high signal intensity T2-weighted images predictive of good response. **Efficacy** Mean reduction fibroid volume 95% CI 2 month 43% (6%, 100%) 6 months 59% (6%, 100%) 2 months larger 40% (24%, 52%) smaller 60% (28%, 78%) No complications reported

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Chrisman 2000[55] USA Two-centres: 1 community hospital; 1 major tertiary care university medical centre **Date** April 1998 Sept 1999 **Funding**: None declared	**>one centre case series** prospective **Patients**: 66 **Mean age**: 44 (30-55) Refused surgical intervention; Poor candidates for myomectomy. Did not desire future fertility; or option other than UAE hysterectomy only. **Pre-UAE –** Clinical and biochemical tests **Post-UAE** Follow up 2 weeks, 3,6 and 12 months Repeat tests	**Included:** Patients with diagnosis of symptomatic fibroids confirmed by gynaecological examination; clinical consultation with interventional radiologist and nurse practitioner. Menorrhagia; progressive or abdominal distension or discomfort; Otherwise candidates for surgical resection Excluded- Peri-menopausal symptoms defined by >20 IU/L FSH irregular menses; hot flushes or night sweats.	66 Bilateral 355-700 *u*m dia Polyvinyl alcohol foam particles	Standard questions Effect on ovarian function by two age groups: n= 45 Less than 45 years n= 21 45 years and older Statistical differences chi^2 test	Mean follow up 11 months (range, 6-17 months) **Efficacy** 56/66 resumed regular menses Mean 3.5 (range, 1-8) weeks **Safety** 10/66 did not resume regular menses. 9/10 findings consistent with ovarian failure 1/10 Surgical gelatin pledget embolization only; amenorrhoea FSH (<20 IU/L) 9/21 aged 45 years and older; 0/45 aged under 45 years No differences between those who did and did not resume regular menses for presenting symptoms; fibroid size; amount of PVA used. Post UAE ovarian failure significantly more likely to occur in patients aged 45 and over than in younger patients. No results by different centres reported. No other safety or efficacy data reported.

Study	Design/Patients	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Colgan 2003[50] Canada Multi-centre 8 settings: University and community hospitals **Date** Not reported **Funding**: None declared	**Case series** Prospective Consecutive patients **Patients**: 555 **Mean age**: 43 (18-59) 66% Caucasian 23% Black 11% Other ethnic origin 31% <40 years old 68% university educated 85% working outside home Black women significantly -- younger (40.7 years vs. 44.0 years); - more likely to have multiple fibroids. Mean fibroid volume 293 (95% CI 259-327 cm^3) Length 8 (range, 1-24 cm) Mean uterine volume 680 (95% CI 626-734 cm^3) Length 14 (range, 5-30 cm) No differences in uterine/fibroid size for age or ethnicity. 268/537 no children; 164/537 Fertility an issue **Pre UAE** Ultra-sound Questionnaires Gynaecological examination	**Included**: 355/539 multiple fibroids 80 Pre-menopausal Symptomatic fibroids sufficiently severe for hysterectomy. Average 5 years duration 3 previous consultations with gynaecologists, 10 physicians 80% heavy menstrual bleeding; 73% urinary urgency/frequency 41% pain during intercourse 40% work absences 439 fibroid impact on life score 4 or higher. 101 previous treatment for fibroids. 19% other major health problems. 5% increased surgical risk. Younger women – poorer self-perceived health status; 35% overweight; 17% obese **Excluded** Pelvic inflammatory disease Undiagnosed pelvic mass Endometrial carcinoma Pregnancy; renal insufficiency	538 Bilateral 14 Unilateral 11 interventional radiologists **Primary Embolising material** Polyvinyl alcohol particles 355-500 *u*m dia. Gelfoam used by 4 InterventionalRadiologists in 57% of their cases Average procedure time: 61 mins **Endpoint** Standing column of contrast or contrast refluxed toward uterine artery or into internal iliac artery	3 months follow-up; median 8.1 months Blinded to indications for surgery or time elapsed since UAE. Histologic review of excised tissue.	Selected results – see Pron[48], Pron[49] and Pron[51] **Safety** Treatment failure or clinical failure 17/ 18 women: (2 myomectomy; 16 hysterectomies) PVA emboli in post UAE specimens from 17/18 cases 1/18 case without embolic material identified in histological review was a large viable cervical rather than uterine body leiomyoma – Clinical history indicated that location of fibroid was not appreciated before UAE

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De Souza 2002[20] UK Single-centre **Date** N/R **Funding**: None declared	**Before and After** Prospective case series **Patients**: 11 **Mean age**: 40 (29-48) 45 fibroids in total - Volume mean 89.9 cm^3 (0.6-434) median 41.2 cm^3 34 myometrial location; 7 submucous; 3 subserosal 1 cervical **Pre-UAE –** MRI Postal questionnaire FSH tests **Post-UAE** MRI images: 1 day; 1 and 4 months; FSH tests 4 months Postal questionnaire 12 months	**Included:** Consecutive patients with diagnosis of fibroids 11/11 Menorrhagia; 8/11 Abdominal distension/feeling of mass	11/11 bilateral **Embolizing material**: 355-500 *u*m dia. Polyvinyl alcohol particles **Post-op care** 9/11 intravenous analgesia for pain	Mean reduction in: fibroid volume; dominant fibroid volume; uterine volume FSH level Postal questionnaire symptom scores before and after UAE. Each symptom scored 1-3 to produce final total of 9. Formula to assess change in clinical score at 12 months follow up: Difference in follow upscore/ Preembolisation score x 100.	**Efficacy** Mean reduction fibroid volume 4 months 38.2% ± 25.2% Mean reduction volume dominant fibroid 1 day 6% ± 8.1% 1 month 22.3% ± 17.5% 4 months 36.7% ± 26.5% Mean reduction uterine volume 4 months 20.1% ± 22.6% FSH levels: Stable Pre-UAE: 4.9 IU/L ± 2.2 4 months: 5.1 IU/L ± 1.6 Improvements in symptom scores at 12 months: 4/11 56% 4/11 33%-44% 1/11 22% 1/11 11% 1/11 0% Immediate volume reduction in dominant fibroid correlates with improvements/changes in clinical scores at 12 months. Reductions in fibroid volume at 4 months do not. No safety data reported

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Fleischer 2000[63] USA Single-centre **Date** N/R **Funding**: None declared	**Before and After** **Patients**: 20 **Mean age**: 43 (38-57) 4/20 previous transfusions for chronic anaemia 31 fibroids > 2 cm 17 intramural 9 subserosal 4 submucosal 1 cervical **Pre-UAE –** 3D color-doppler sonography one hour before UAE **Post-UAE** 3D color-doppler sonography 1 day, 3 and 6 months	**Included:** Patients referred for UAE Symptomatic fibroids 6 months to one year duration including: Abnormal uterine bleeding; Abdominal discomfort; Urinary frequency – bulk-related symptoms	20 unilateral (both right and left uterine arteries) **Embolizing material:** 355-500 *u*m dia polyvinyl alcohol particles **Endpoint**: statis Secondary embolizing agent*:* Selective gelfoam pledgets.	Mean reduction in: fibroid volume; Changes in vascularity;	**Efficacy** Mean changes: One day post UAE: Reduced vascularity 46% ± 17% 10/12 hypervascular fibroids 50% 4/10 isovascular 50% 2/9 hypovascular fibroids 50% 3-6 months: Increased vascularity 12% ± 14% Reductions in fibroid volume 3 months 22% 6 months 47% Hypervascular fibroids on pre-UAE reduced in size more than other fibroids. 19/20 ‘marked reductions’ in symptoms 95% **Safety** 1/20 elected hysterectomy excessive pain 5%

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Jha 2000[64] USA Single-centre **Date** N/R **Funding**: Grants from Siemans Medical Systems and Berlex Laboratories	**Before and After** **Patients**: 31 **Mean age**: 45.2 (31-53.8) 125 fibroids in total **Pre-UAE –** MR <one month before UAE **Post-UAE** MR images: 3 and 12 months (assessed by 3 readers other than operating IR) Symptom questionnaire 3 months	**Included:** Consecutive patients with symptomatic fibroids: 18 bleeding and pelvic pain; 11 bleeding; 2 pain Failed medical treatment 4 previous myomectomy. **Excluded**: Patients for whom a myomectomy was a simple therapeutic option; wished to maintain fertility	16/18 bilateral 2/18 unilateral Experienced interventional radiologist 500-710 *u*m dia. polyvinyl alcohol particles	Mean reduction in: fibroid volume; vascularity; Symptom relief measures: (pelvic pain or bleeding): 1 Better 2 No Change 3 Worse	**Pre-UAE MRI** high signal intensity T1-weighted images predictive of poor response; high signal intensity T2-weighted images predictive of good response. Strong predictor of good response: • Submucosal location. • Hypervascular fibroids Predictor of poor response: • Increasing age • Increasing pre-treatment uterine volume **Efficacy** Mean reduction 3 months uterine 33.5% ± 16.1% (SD) p<0.001 fibroid 40.4% ± 35.8%(p<0.001) Mean reduction one year (5 patients only) fibroid 64.06% ± 30.30% 26/31 improvement 84% 4/31 no improvement in one or more symptoms: 1/4 adenomyosis; 13% 1/31 worsening 3% **Safety** 2/31 hysterectomy 6%

Study	Design/Patients	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Klein 2001[65] USA Single-centre **Date** July 1998-ongoing at date of publication **Funding**: Northwest Kaiser Permanente (a closed–panel health maintenance organisation >400,000 members)	**Case series** Prospective **Patients**: 35 Highly motivated. Mostly specific request for UAE **Mean age**: 46 (32-56) 13 nulliparous; 8 primiparous 14 multiparous **Pre-UAE**: Laboratory tests MRI **Follow-up**: Telephone interviews 6 weeks and 6 months; U/sound 8 weeks and 6 months	**Included** Symptomatic fibroids assessed by MRI and gynaecological examination in accord with protocols. Significant symptoms heavy bleeding, pelvic pressure, urinary frequency. **Excluded** Pelvic pain only Desire for future fertility and only one or two myomas	Outpatient ambulatory care unit **Embolizing material** 350-500 *u*m dia. polyvinyl particles mixed with saline and iodinated x-ray contrast **Secondary embolising agent**: Selective Gelfoam pledgets **Post-UAE care**: 29/35 discharged 6.9 hours (5-10 hours) 6/35 not discharged 3/35 admitted within 1 week post UAE	Reductions in uterine and fibroid volume **Symptoms** Subjective satisfaction expressed by patients	**Efficacy** reduction 6 months***** *24 patients* Mean Uterine 36% (11%-30%) Dominant fibroid 49% (1%-92%) Statistically significant changes **Patient satisfaction** 6 months***** *30 patients* 26/30 Very satisfied 87% 4/30 Unsatisfactory 13% 2 no improvement; 1 subsequent surgery 1 technical failure and repeat UAE **Safety** Pain 21/29 Intravenous analgesia Ovarian function 4/30 (aged 43-51 years) amenorrhoea and elevated FSH 6 months post UAE Figures reported do not take 5 patients lost to follow up into account

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
McLucas 2001[56] USA >one centre **Date** 1996 December 1999 **Funding**: None declared.	**case series** observational clinical study overlaps with McLucas[66] **Patients**: 14*/400 **Mean age**: 41 (26-67) years Average dia. largest myoma 7.5 cm(1.2-19 cm) Average uterine volume 1389 ml (117-8804 ml) 139/400 identified fertility as a goal after UAE **Pre-UAE** FSH levels Clinical assessment **During** radiation exposure **Post-UAE** 6 months FSH Clinical assessment Request to be notified of subsequent pregnancy or procedures or surgeries	**Included** Patients with symptomatic fibroids: menorrhagia or postmenopausal bleeding secondary to uterine myomata. No size restriction on individual myoma or uterine. No treatment on the basis of infertility as a symptom	Not described	Pregnancy and delivery following UAE Effect on ovarian function measured by change in FSH levels and menopausal symptoms	**Safety** 17 pregnancies reported in 14 women 5 sponteneous abortions 10 normal deliveries; 2 pregnant at time of publication. 1/10 premature labour, placenta previous and abruptio placenta, delivered at 32 weeks gestation. 9/10 full term without complications Ovarian function 4/6 women <45 years experienced premature menopause. Normal FSH levels before UAE experienced amenorrhoea and hot flushes post-UAE. Operator competence observed as a potential factor in non-target embolization of ovarian arteries. 2/400 hysterectomy as a result of infection. 1/2 pathology report revealed chronic salpingitis. 1/2 pre-UAE uterine volume of 7932 cm^3 requiring 10.75 vials of 300-500 polyvinyl alcohol particles (PVA) to occlude the uterine arteries (average uterine volume 620.17 cm^3 and 3.62 vials of PVA), did not respond to anti-biotic therapy after abscess was noted on MRI. Radiation exposure – reported McLucas [65] No results reported by different centres. No efficacy data reported

Study	Design/Patients	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
McLucas 2001[66] USA Single-centre **Date** April 1997 August1999 **Funding**: None declared	**Case series** Prospective **Patients**: 167 **Mean age**: 43 (29-63) 2 menopausal 51 previous pelvic surgeries **Pre-UAE**: Ultrasonography Laboratory tests Symptom scores (patient) Bleeding Pain Pressure **Post-UAE**: Ultrasonography (mostly same observer and equipment) <2, 6 and 12 months FSH Interviews 5 months	**Included**: Symptomatic fibroids – predominantly menorrhagia	Community hospital 163 bilateral 4 unilateral **Embolizing material**: Polyvinyl alcohol particles 108 procedures 500 *u*m dia. 60 -do- 300 *u*m dia **Endpoint** 1. Statis – elevated FSH levels noted in some patients. Thereafter 2. Resistance. Wait. Repeat contrast injection – No further FSH change noted **Post-op care**: Bed rest 6 hours	**Reductions in uterine volume** **Symptom scores** Mild Moderate Severe **Definitions:** Improvement going from severe to moderate; Stabilization remaining moderate or mild **'**Failure group**'** Subsequent hysterectomy, or <10% shrinkage in myoma at 6 months, or worsening symptoms at 6 months; Overlapping groups counted as 'one'. **Success = Not failure** **Radiation exposure** Subset of 50 consecutive patients Patient numbers at follow up < 2 months 125 6 months 98 12 months 46	**Efficacy** Volume uterine reduction Follow up n % < 2 months 125 23 6 months 98* 31 12 months 46 37 131/150 improvement or stabilisation of symptoms. 88% 21/167 treatment 'failures' 12% **Safety** 119 Pain; observed overnight 12 Fever; 8/12 contacted physican; 3 readmitted; 6 Hysterectomy; 1/6 sepsis; 4 pelvic pathology noted pre-UAE; 1/6 unknown 8 Expelled necrotic submucous myomas 2-12 months post UAE; 5/8 sponteously; 3/8 vaginal myomectomy to complete passage Radiation 0.9 to 1.1 rads per minute, mean radiation exposure 14 (6.4 - 45.8) minutes. Compare barium enema 6-rad; hysterosalpingogram 2-rad. Proficiency of radiologist important Fertility Ovarian function 4/98* menopause >45 years old 2 successful pregnancies and deliveries post UAE Results reported to not take account of increasing numbers of patients lost to follow up

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Mehta 2002[22] UK Single-centre **Date** June 1998- April2000 **Funding**: None declared	**Case series** Retrospective notes review **Patients**: 7/42 **Mean age**: 42 (31-54) 36 Afro-Caribbean 4 Caucasian; 2 Asian. 38 multiple fibroids 4 single fibroids max dia. 5-22 cm **Pre-UAE** Ultrasound Laboratory tests FSH level Ultrasonography **Post-UAE** Ultrasound and clinical follow up 6 weeks, 6 and 12 months routinely. Otherwise at Gynaecologist's discretion	**Included** Diagnosis of fibroids referred by gynaecologist main symptom 76% menorrhagia or dysmenorrhoea; 24% uterine bulk, urinary frequency **Excluded** Concurrent pelvic infection	Inpatient 41 bilateral 1 unilateral **Embolizing material**: 300-500 *u*m polyvinyl alcohol particles **End-point** Statis **Post-op care** Anaesthetist-led pain control team; All discharged within 48 hours post-UAE	Rates of readmission post UAE	**Safety** 7 readmissions; median time 3 weeks post UAE (range 1-29 weeks); All emergency presentations to A&E – fever and pain. Additionally, 5 had vaginal discharge, and one was unable to pass urine 2/7 admitted twice; 3/7 improved on antibiotic therapy; 3/7 also required manual removal of extruding fibroid; 1/7 total hysterectomy for pyometritis. Mean inpatient stay 12.6 days (range 4-21 days); 1/7 subsequent normal full-term pregnancy 1/7 ovarian failure not considered related to UAE Complications rate 7/42 17% No efficacy results reported

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Messina 2002[78] Brazil Single-centre **Date** March 2000-January 2001 **Funding**: None declared	**Case series** Prospective **Patients**: 26 **Mean age**: 43 (33-49) **Pre-UAE** FSH level Ultrasonography **Post-UAE** Clinical follow up 1 week; 3 and 12 months Ultrasonography	**Included** Diagnosis of fibroids confirmed by ultrasonography and gynaecological examination Heavy menstrual bleeding Pelvic pain or pressure Refused surgical treatment Pre-menopausal **Excluded** FSH level 30 IU/1 and clinical indications of menopause	Inpatient 24/26 bilateral 2/26 unilateral **Embolizing material**: 500-710 *u*m polyvinyl alcohol particles **End-point** Complete vascular occlusion	Laboratory Mean reduction in: uterine volume; Clinical improvement Effectiveness by standard questions Hemoglobin levels FSH level Pain visual analogue scale	**Efficacy** % reduction uterine volume: Median Mean Range 3 months 27.9 29.4 11-65 1 year 45.4 41.1 2-91 All changes p<0.001 21/24 menorrhagia and anaemia controlled; Hemoglobin : 2.6 g/dl 1 year post UAE 88% 16/19 pelvic pain/pressure improved 84% 1/26 technical failure 4% **Safety** 3/26 treatment failures requiring hysterectomies: 12% 1 unremitting pelvic pain, vaginal bleeding – adenomyosis noted; 1 fever, pain, elevated white blood cell count, vaginal discharge and expulsion of infected uterine fibroid – 3 months post-UAE;. 1 submuscosal fibroid – persistent heavy bleeding. Fertility 3/26 ovarian failure 1 <45: 2 >45 years

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Nevadunsky 2001[67] USA Single-centre **Date** August 1998 August 1999 **Funding**: None declared	**Patient survey** Prospective Consecutive patients **Patients**: 84 **Mean age**: 44 (27-56) 60/84 Caucasian (71%) 59/84 College or postgraduate degree (70%) 57/84 Household income > $50,000 (68%) 49/84 Household income > $75,000 (58%)	**Included:** Presenting for UAE for symptomatic fibroids Excessive bleeding (61) anaemia (41) pelvic pain (29) Pressure (21) bulk related symptoms 24 Otherwise candidates for surgical resection	N/A	Ranking of priorities in decision to seek UAE by numbers of responses Source of information Impact on quality of life Decision-making determinants	Symptoms significant impact on quality of life. Information 56/84 used Internet 34/84 Literature primary source of information about UAE Knowledge of fibroids 79/84 well-informed Knowledge of treatment options 82/84 well-informed Impact of fibroids on quality if life Worries about health; daily discomfort; anxiety; limits daily activities; limits sexual activity; cause of sadness or depression; limits social activity Decision-making determinants in >50% of sample: Avoid recurrence of fibroid symptoms Avoid adverse effects of alternatives Avoid prolonged surgical recovery Avoid any surgical intervention No safety or efficacy data

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Nikolic 2000[68] USA Single-centre **Date** N/R **Funding**: None declared	**Case series** Prospective **Patients**: 20/23 **Mean age**: 43.7 (30-53) Estimating risks of radiation dose during UAE with known risks from other souces Data collected during UAE	**Included**: Patients undergoing UAE **Excluded**: Unreliable data showing inconsistent vaginal and skin dose measurements (ie lower than average yet higher exposure numbers and long fluoroscopic times)	2 unilateral 21 bilateral **Embolizing material:** 500-700 *u*m dia polyvinyl alcohol particles **Endpoint**: statis and slight antegrade flow still present in uterine artery	Estimate of genetic risk from radiation dose. Fluoroscopic times; Radiation absorbed by skin; Radiation absorbed by ovaries; Population estimates based on numbers of patients who undergo hysterectomy for fibroids in US annually; numbers of women of child-bearing age, and average numbers of children.	**Safety** <u>Mean times/dose</u>: Fluoroscopic time 21.89 minutes (range 8-52.5); Radiation dose 2.9 R/min (0.75 mC/kg/min) to 4.4 R/min (1.13 mC/kg/min); Numbers of exposures 44 (range, 21–62); Ovarian dose 22.34 cGy (range 4.25-65.08 cGy); Skin dose 162.32 cGy (range 66.01-303.89 cGy); Genetically significant dose 0.005 mSv Population estimates and comparison with known risks of radiation from <u>other sources:</u> Genetically significant dose 0.23 mSv (23 mrem) Contribution of UAE 2.2% to genetically significant dose from medical applications. Contribution of UAE to total genetically significant dose 0.4% Fluoroscopy times and numbers of exposures reduced with numbers of UAE performed. UAE not likely to result in radiation-induced skin effects, or substantial increased risk to future children. Fertility Effects on ovarian function uncertain. 1/23 repeat UAE

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Omary 2002[69] USA Single-centre **Date** Feb-Jun 2001 **Funding**: RSNA Bracco Diagnostics Award and NIH; RSNA research and education fund medical student	**Before and After MRI** Prospective **Patients**: 60 **Radiologists:** 5 **Mean age**: 44 (31-54) (patients) **Pre-UAE**: (physician) 1) Pre-MRI scan questionnaire with diagnostic options: uterine fibroids; adenomyosis; endometrial masses; adnexal masses; cervical masses; other (specifiy); multifactorial; normal. **Post-MRI**: 1) Review of diagnosis and anticipated treatment plan by IR and MR imaging specialists 2) Post-MRI questionnaire	**Included:** (patients) Previous diagnosis of fibroids; significant uterine bleeding; bulk-related symptoms; and/or pain. **Excluded**: Disinterested in UAE; Strong desire for future fertility; History of severe reactions to iodinated contrast agents; Currently pregnant.	Inpatient university-affiliated tertiary care medical centre Procedure not reported	Pre UAE : Changes in planned treatment and actual treatment as measure of diagnostic confidence	**Safety and efficacy** Pre- MRI 57/60 intended for UAE; Post-MRI 10/57 assigned to different treatment plan; 8/10 from UAE to surgery. 17.5% No UAE treatment outcomes data reported

Study	Design/Patients	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Pelage 2000[57] France Single-centre **Date** June 1991- December 1996 **Funding**: None declared	**Case series** Prospective **Patients**: 80 **Mean age**: 44.7 (30-54) 63 intramural location mean dia. largest fibroid 58 (range 21-100) mm 15 previous myomectomy **Pre-UAE**: Ultrasonography **Post-UAE**: 1, 6,12 and 24 months; annually thereafter. Ultrasonography Gynaecologic examination 4-7 weeks and regularly thereafter 5-point Symptom scale (complete resolution to worsening)	**Included**: Failed medical treatment; Otherwise planned hysterectomy or myomectomy. Main criterion for UAE: refractory vaginal bleeding; Most frequent symptom pelvic pain; anaemia.	Inpatient 76 Bilateral 4 Unilateral 5 vascular radiologists procedure time 45-90 minutes **Embolizing material**: Polyvinyl alcohol particles 150-300 *u*m **Endpoint**: 1 no residual hypervascularisation visible; 2 statis – distal; 3 reduced flow – proximal. **Secondary embolising agent**: None **Post-op care**: Obs & Gynae Ward Post embolization pain protocols; patient-controlled pump. Discharge 1-2 days	**Reductions in fibroid volume** **Change in symptoms** **Symptom scale**: 5-category scale (bleeding and pelvic pain): 1 complete resolution 2 significant improvement 3 slight improvement 4 unchanged 5 worsened	**Efficacy** Volume reduction dominant fibroid 2 months 6 months Mean 20% 52% Latest follow up 72/80 complete resolution 90% 3*/80 marked improvement 4% 5*/80 no improvement 6% **1/3 and 3/5 unilateral procedures* 74 – normal menstruation first cycle **Safety** 68/80 intense pain 6/80 post embolization syndrome 4/80 expelled necrotic fragments of a pedunculated submucosal myoma <1 month UAE. Fertility 4/80 transient amenorrhoea 2/80 permanent amenorrhoea

Study	Design/Patients	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Pelage 2003[58] France Single-centre **Date** >48 months before publication **Funding**: Post study Research grants Biospher Medical	**Case series** Prospective **Patients**: 20 15 white; 5 black 12/20 intramural fibroids 8/20 mixed fibroids **Mean age**: 43.1 (36-53) **Pre-UAE**: 20/20 Ultrasound and 9/20 MRI **Follow-up**: 1, 6,12 and 24 months; annually thereafter. Telephone interviews	**Included**: Failed medical treatment; No desire for future pregnancy unless only surgical option hysterectomy; Pre-menopausal; Heavy menstrual bleeding 20/20; Iron deficiency 11/20 Pelvic pain/pressure 9/20 **Excluded**: Single submuscosal or pedunculated subserosal fibroids	Inpatient Bilateral **Embolizing material**: calibrated microspheres 700-900 *u*m dia. **Endpoint**: 4 no residual hypervascularisation visible; 5 statis – distal; 6 reduced flow – proximal. **Secondary embolising agent**: None **Post-op care**: Admission to Obs & Gynae Ward Post embolization pain protocols Discharge 1-2 days	**Symptom scale**: 5-category scale (bleeding and pelvic pain): 1. complete resolution 2. significant improvement 3. slight improvement 4. unchanged 5. worsened **Major complications**: Menstrual irregularity/amenorrhoea Pelvic infection Expulsion necrotic fragments **Minor complications**: Allergy to contrast medium adverse drug reaction groin haematoma dissection of uterine artery	**Efficacy 6 months :** Volume reduction Uterine Dominant Median 36 81 Mean 34 43 Latest follow-up (bleeding): % 17/20 Complete resolution 85 1/20 Significant Improvement 5 1/20 No change 5 1/20 Worsened 5 1/20 Repeat UAE **Safety** 5/20 No pain 11/20 Moderate pain; 1/11 delayed intense pain 3 days post UAE readmission intravenous pain control; 4/20 Intense pain; 1/20 Expulsion necrotic fragments two and seven months post-UAE; Fertility 1/20 Pregnancy and delivery 1/20 (53 years) menstrual irregularity - 9 months post UAE;

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Pinto 2003[45] Spain Single-centre **Date** April 1999 – June 2001 **Funding**: None declared	**Prospective Randomised Controlled Trial** using Zelen's pre-consent design Interventions: Group 1 UAE or hysterectomy Group 2 hysterectomy only Safety and efficacy results were reported for n=40 patients who had UAE **Mean age** 43 (18-59) **Pre-UAE** Laboratory tests MRI **Post-UAE** MRI Patient-reported clinical change Patient satisfaction 2-year follow up	**Included** Patients with bleeding fibroids who were candidates for surgical resection **Excluded** Desire to maintain fertility Fibroids >10 cm dia. Contraindications for surgery Sensitivity to iodine-based contrast material	Inpatient – 450-bed teaching hospital 35 bilateral 5 unilateral All procedures same two InterventionalRadiologists **Embolizing material** 400-600 *u*m dia polyvinyl alcohol particles	Bleeding cessation; Length of hospital stay; Complications **Recovery – 4 pt. scale** Full – cessation of menorrhagia or metrorrhagia or either if one only; Partial – Reduced menorrhagia; No improvement – no change; Worsening **Complications** Minor - no consequences for patient except nominal treatment; Moderate - non-life threatening additional treatment without sequelae for patient (post embolization syndrome, urinary infection); Major - death or life-threatening. **Satisfaction** Would you undergo UAE again?	**Efficacy** UAE Clinical success (improved bleeding) 31/39 Mean volume reduction at 6 months in Dominant fibroid 46% (27%,66%) **Safety** <u>UAE</u> 29/40 complications <30 days 73% >one complication x 9 patients 2 readmitted to hospital – post embolization syndrome; severe pelvic pain. major complication x 1 patient <u>Hysterectomy</u> 9/20 complications <30 days; 45% >one complication in 3 patients; 1 patient readmitted for transfusion. major complications <u>≥</u>4 patients **Satisfaction** UAE Hysterectomy 28 Yes 15 3 Maybe 5 No 2 4 Not reported 3

Study	Design/Patients	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Pron 2003[47] Canada Multi-centre 8 settings: University and community hospitals **Date** Not reported **Funding**: None declared	**Case series** Prospective Consecutive patients **Patients**: 555 **Mean age**: 43 (18-59) 66% Caucasian 23% Black 11% Other ethnic origin 31% <40 years old 68% university educated 85% working outside home Black women significantly -- younger (40.7 years vs. 44.0 years); - more likely to have multiple fibroids. Mean fibroid volume 293 (95% CI 259-327 cm^3) Length 8 (range, 1-24 cm) Mean uterine volume 680 (95% CI 626-734 cm^3) Length 14 (range, 5-30 cm) No differences in uterine/fibroid size for age or ethnicity. 268/537 no children; 164/537 Fertility an issue	**Included**: 355/539 multiple fibroids 80 Pre-menopausal Symptomatic fibroids sufficiently severe for hysterectomy. Average 5 years duration 3 previous consultations with gynaecologists, 10 physicians 80% heavy menstrual bleeding; 73% urinary urgency/frequency 41% pain during intercourse 40% work absences 439 fibroid impact on life score 4 or higher. 101 previous treatment for fibroids. 19% other major health problems. 5% increased surgical risk. Younger women – poorer self-perceived health status; 35% overweight; 17% obese **Excluded** Pelvic inflammatory disease Undiagnosed pelvic mass Endometrial carcinoma Pregnancy; renal insufficiency	Pre-UAE Baseline questionnaires; Ultrasound examination	No clinical outcomes reported	539/555 completed questionnaires. Description of Patient population

Study	Design/Patients	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Pron 2003[48] Canada Multi-centre 8 settings: University and community hospitals **Date** Not reported **Funding**: In part Boston Scientific Corporation	**Case series** Prospective Consecutive patients **Patients**: 555 **Mean age**: 43 (18-59) 66% Caucasian 23% Black 11% Other ethnic origin 31% <40 years old 68% university educated 85% working outside home Black women significantly -- younger (40.7 years vs. 44.0 years); - more likely to have multiple fibroids. Mean fibroid volume 293 (95% CI 259-327 cm^3) Length 8 (range, 1-24 cm) Mean uterine volume 680 (95% CI 626-734 cm^3) Length 14 (range, 5-30 cm) No differences in uterine/fibroid size for age or ethnicity. 268/537 no children; 164/537 Fertility an issue **Pre UAE** Ultra-sound Questionnaires Gynaecological examination	**Included**: 355/539 multiple fibroids 80 Pre-menopausal Symptomatic fibroids sufficiently severe for hysterectomy. Average 5 years duration 3 previous consultations with gynaecologists, 10 physicians 80% heavy menstrual bleeding; 73% urinary urgency/frequency 41% pain during intercourse 40% work absences 439 fibroid impact on life score 4 or higher. 101 previous treatment for fibroids. 19% other major health problems. 5% increased surgical risk. Younger women – poorer self-perceived health status; 35% overweight; 17% obese **Excluded** Pelvic inflammatory disease Undiagnosed pelvic mass Endometrial carcinoma Pregnancy; renal insufficiency	538 Bilateral 14 Unilateral 11 InterventionalRadiologists **Primary Embolising material** Polyvinyl alcohol particles 355-500 *u*m dia. Gelfoam used by 4 InterventionalRadiologists in 57% of their cases Average procedure time: 61 mins **Endpoint** Standing column of contrast or contrast refluxed toward uterine artery or into internal iliac artery	3 months follow-up Changes in volume : Uterine/Dominant fibroid **Clinical outcomes** 7-point Symptom score (much worse – much improved) the rating scale was not tested 10-point Life impact score (1 minimal-10 maximum) Menstrual flow and days **Patient satisfaction** Willingness to undergo UAE if necessary; 6-point scale Overall satisfaction; (greatly dissatisfied – greatly satisfied).	Selected results – see Pron[49], Colgan[50] and Pron[51] 526/538 bilateral UAE patients. **Efficacy** Volume change / Median / Mean Dominant fib. / 42% / 33% (95% CI 28-38) Uterine / 35% / 27% (95% CI 23-32) Pre-treatment size Larger fibroids – mean reduction >400 cm^3 Smaller fibroids – mean reduction $\leq$ 200 cm^3 ($p < 0.0001$) Symptom improvement / Mean / 95% CI Menhorrhagia / 83% / (80-87) Dysmenorrhea / 77% / (72-82) Bulk symptoms / 84% / (80-87) Urinary urgency / 86 / (82-90) **Life impact** Pre-UAE 72% score of > 7; Post-UAE 11% - strong association with improvements in menstrual bleeding but not reductions in uterine volume **Safety** Selected complications reported – see Pron[49];Colgan[50] and Pron[51] Amenorrhoea – age dependent <40 years 3% (95% CI 1-7) 40-49 years unreported $\geq$50 41% (95% CI 26-58) **Patient satisfaction** 91% satisfied (95% CI 89-94) 85% (n=414) willing to undergo UAE again if necessary; 93/414 only conditionally so. Efficacy rates reported for sub-set of 526/538 patients Adverse events see Pron[49] and Pron [51]

Study	Design/Patients	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Pron 2003[49] Canada Multi-centre 8 settings: University and community hospitals **Date** Not reported **Funding**: In part Boston Scientific Corporation	**Case series** Prospective Consecutive patients **Patients**: 555 **Mean age**: 43 (18-59) 66% Caucasian 23% Black 11% Other ethnic origin 31% <40 years old 68% university educated 85% working outside home Black women significantly -- younger (40.7 years vs. 44.0 years); - more likely to have multiple fibroids. Mean fibroid volume 293 (95% CI 259-327 cm^3) Length 8 (range, 1-24 cm) Mean uterine volume 680 (95% CI 626-734 cm^3) Length 14 (range, 5-30 cm) No differences in uterine/fibroid size for age or ethnicity. 268/537 no children; 164/537 Fertility an issue **Pre UAE** Ultra-sound Questionnaires Gynaecological examination	**Included**: 355/539 multiple fibroids 80 Pre-menopausal Symptomatic fibroids sufficiently severe for hysterectomy. Average 5 years duration 3 previous consultations with gynaecologists, 10 physicians 80% heavy menstrual bleeding; 73% urinary urgency/frequency 41% pain during intercourse 40% work absences 439 fibroid impact on life score 4 or higher. 101 previous treatment for fibroids. 19% other major health problems. 5% increased surgical risk. Younger women – poorer self-perceived health status; 35% overweight; 17% obese **Excluded** Pelvic inflammatory disease Undiagnosed pelvic mass Endometrial carcinoma Pregnancy; renal insufficiency	538 Bilateral 14 Unilateral 11 interventional radiologists **Primary Embolising material** Polyvinyl alcohol particles 355-500 *u*m dia. Gelfoam used by 4 InterventionalRadiologists in 57% of their cases Average procedure time: 61 mins **Endpoint** Standing column of contrast or contrast refluxed toward uterine artery or into internal iliac artery	2 weeks; 3 months follow-up; median 8.1 months Complications resulting in hysterectomy Histopathology reports on excised tissue	Selected results – see Pron[48], Colgan[50] and Pron[51] **Safety** 8 hysterectomies following complications (3 within one month; 5 within three months); 6 total hysterectomies; 2 sub-total hysterectomies. 2 Emergencies following infection; 4 Pain; 1 prolapsed myoma; 1 persistent vaginal bleeding. 8/8 fibroids intramural location and also 4/8 subsrosal. 4/8 performed at institutions other than UAE study institutions. PVA found in excised tissue.

Study	Design/Patients	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Pron 2003[51] Canada Multi-centre 8 settings: University and community hospitals **Date** November 1998 and November 2000 **Funding**: None declared	**Case series** Prospective Consecutive patients **Patients**: 555 **Mean age**: 43 (18-59) 66% Caucasian 23% Black 11% Other ethnic origin 31% <40 years old 68% university educated 85% working outside home Black women significantly -- younger (40.7 years vs. 44.0 years); - more likely to have multiple fibroids. Mean fibroid volume 293 (95% CI 259-327 cm^3) Length 8 (range, 1-24 cm) Mean uterine volume 680 (95% CI 626-734 cm^3) Length 14 (range, 5-30 cm) No differences in uterine/fibroid size for age or ethnicity. 268/537 no children; 164/537 Fertility an issue **Pre UAE** Ultra-sound Questionnaires Gynaecological examination	**Included**: 355/539 multiple fibroids 80 Pre-menopausal Symptomatic fibroids sufficiently severe for hysterectomy. Average 5 years duration 3 previous consultations with gynaecologists, 10 physicians 80% heavy menstrual bleeding; 73% urinary urgency/frequency 41% pain during intercourse 40% work absences 439 fibroid impact on life score 4 or higher. 101 previous treatment for fibroids. 19% other major health problems. 5% increased surgical risk. Younger women – poorer self-perceived health status; 35% overweight; 17% obese **Excluded** Pelvic inflammatory disease Undiagnosed pelvic mass Endometrial carcinoma Pregnancy; renal insufficiency	538 Bilateral 14 Unilateral 11 interventional radiologists **Primary Embolising material** Polyvinyl alcohol particles 355-500 *u*m dia. Gelfoam used by 4 interventional radiologists in 57% of their cases Average procedure time: 61 mins **Endpoint** Standing column of contrast or contrast refluxed toward uterine artery or into internal iliac artery	Technical success: All fellowship-trained in vascular and interventional radiology and at least 3 years experience in peripheral angiography and embolisation techniques. 2/11 dedicated interventional practice.	Selected results – see Pron[47], Pron[48]; Colgan[50] and Pron[51] **Efficacy** 570 UAE procedures in 555 patients. 97% technical success bilaterally.(538 patients) Main reason for technical failure : variant anatomy **Safety** 30 adverse events (30/555) Complication rate 5.3% (95% CI 3.6-7.4) 3 major complications: (1 multiple seizures; 2 serious allergic reactions) 4 perforations; 10 minor Significant variation between: - Interventional radiologists in both times ($p < 0.001$); - Successes and failures, and - First 20 and next 20 procedures Mins/Procedure 95% CI / Mins/Fluoroscopy 95% CI Successes 61.0 (58-63) / 18.9 (18-19.8) Failures 88 (75-100) / 31.5 (24.3-38.6) First 20 procedures 75 (95% CI 70-80) / 21.3 (19.4-23.3) Next 20 procedures 55 (95% CI 52-59) / 16.2 (14.8-17.5) Adverse events rate 5.3% 30/555 Efficacy rates[48] reported for sub-set of 526/538 patients

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Ravina 2000[59] France One centre **Date** 1988 December 1997 **Funding**: None declared	**case series** prospective observational clinical study **Patients**: 9*/184 **Mean age**: 36* (22-41) median 40* 3/9 one large myoma 6/9 3 or more dia. range 40 to 100 mm	**Included:** Patients becoming pregnant following UAE for symptomatic fibroids	Highly selective and bilateral **Embolizing materials** 150/300 to 300/600*u*m dia Polyvinyl alcohol foam particles	Pregnancy course and delivery following UAE Delay to pregnancy Maternal blood pressure Fetal growth Possible recurrences of myoma Sonographic exam/monthly Fetomaternal vascularization Age and term of pregnancy Miscarriages Premature birth Delivery mode Birth weight and post-partum course	**Safety** 12 pregnancies in 9 women 5 early miscarriages in 3 women 8 infants delivered in 7 pregnancies 1 patient died severe AIDS and streptococcal septicaemia at 28 weeks. Infant died subsequently. Delay to pregnancy: 13 (range, 4 to 23) months Age at delivery: 38 (range, 23 to 43) years Miscarriages: 5 in 3 patients >40 (40-42 years) Infants: 8 in 7 patients (one twin) Term: 4 full term; 3 premature Delivery: 3 vaginal; 4 cesarean sections Recurrence of myoma: None

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Razavi 2002[54] USA Single-centre **Date** July 1998- December 2000 **Funding**: None declared	**ComparativeCase series** Retrospective notes review **Patients**: 67/111 (UAE/all) Strong desire to avoid hysterectomy **Mean age**: 44 (31-56) **Pre-UAE** Gynaecological examination Routine history Laboratory tests Pelvic imaging – sonography or MRI **Post-UAE** Mean follow up 14.3 months. Telephone questionnaire Review of medical records	**Included** Menorrhagia, pain, pressure, pelvic discomfort, mass effect causing abdominal distension or urinary tract symptoms 52 bleeding 34 pelvic pain 37 mass effect	Inpatient 66 bilateral 1 unilateral **Embolizing material**: 300-500 *u*m polyvinyl alcohol particles or 500-700 *u*m Trisacryl gelatin microsphere **End-point** Statis	**Changes in symptoms**: Menhorrhagia, pain, mass effect assessed on 6-point scale: 6 Complete resolution 5 Significant resolution 4 Moderate 3 No change 2 Moderately worse 1 Significantly worse Time to resumption of daily activities Pain control **Major complications** leading to death, additional procedures; prolonged hospital stay; undesirable outcome or clinic visits within 30 days; bleeding leading to transfusion	**Efficacy** Significant or complete resolution of symptoms achieved* *62 patients* 48/52 menorrhagia; 92% 25/34 pain 73% 28/37 mass 76% 5 further interventions- 3 mymomectomies; 2 hysterectomies Mean time to resume normal activities 8 days (range 1-49 days); Pain control 5.1 days (range 1-21 days) **Safety** 7 complications – 11% 1 readmission for endometritis; 1 readmission for pelvic pain; 1 transient numbness in groin access site; Fertility 4 menopause >46 years old

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Ryu 2001[70] USA one centre **Date** May 2000 December 2000 **Funding**: Cardiovascular and Interventional Radiology Research and Education Foundation (CIRREF).	**case series** Prospective **Patients**: 23 **Mean age**: 42.6 (35-51) years **Pre-UAE** Gray-scale and color Doppler US **Post-UAE** Gray-scale and color Doppler US Clinical visit Telephone contact *17 completed study*	**Included** Consecutive patients with symptomatic fibroids: menorrhagia and/or bulk-related symptoms. **Excluded** Menopausal and post menopausal symptoms specifically hot flashes or night sweats.	Bilateral selective **Embolizing materials** Polyvinyl alcohol particles 355-500 *u*m dia. in 19 patients 500-700 *u*m dia. 2 patients. Embosphere 500-700 *u*m dia. 2 patients **Endpoint** Statis in the spiral uterine artery branches with antegrade flow in main uterine artery.	Changes in ovarian function as measured by increased vascular impedance by arterial signal or increase in RI and PI. Resistive Index = PSV-EDV)/PSV Pulsatibility Index = (PSV – EDV/mean Menopausal symptoms on questionnaire – hot flushes, mood swings, vaginal dryness, post-coital bleeding, weight gain, and bleeding >once every 3 weeks. Statistical significance p 0.05 or less.	**Safety** Fertility Significant increase in vascular impedance 15/17 patients ($p<0.001$) immediately post-UAE 9/17 complete loss of Doppler arterial signal in the ovary after UAE. 6/8 remaining (n=17) RI and PI values increased. 2/8 RI and PI values decreased. Evidence of significant vascular derangement in ovarian arterial circulation immediately after UAE. Mechanism unknown – inadvertent embolization not ruled out. See Ryu[71]

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Ryu 2003[71] USA one centre **Date** May 2000 December 2000 **Funding**: Cardiovascular and Interventional Radiology Research and Education Foundation (CIRREF).	**case series** Prospective **Patients**: subset of 6/23 (see Ryu[70]) **Mean age**: 40 (35-51) years **Pre-UAE** Gray-scale and color Doppler US **Post-UAE** Gray-scale and color Doppler US Clinical visit Telephone contact Mean follow up 28 (range, 18-42 weeks)	**Included** Complete loss of ovarian function post UAE as measured by increases in RI and PI values and arterial signal in a previous study to assess ovarian arterial perfusion[69].	Bilateral selective **Embolizing materials** Polyvinyl alcohol particles 350-500 *u*m dia. in 3 patients 500-700 *u*m dia. 2 patients. Embosphere 500-700 *u*m dia. 1 patients **Endpoint** Statis in the spiral uterine artery branches with antegrade flow in main uterine artery.	Changes in ovarian arterial perfusion at follow up measured by increased vascular impedance by arterial signal or increase in RI and PI. Resistive Index = PSV-EDV)/PSV Pulsatibility Index = (PSV – EDV/mean Menopausal symptoms on questionnaire – hot flushes, mood swings, vaginal dryness, post-coital bleeding, weight gain, and bleeding >once every 3 weeks. Statistical significance p 0.05 or less.	**Safety** Fertility 4/6 re-established arterial perfusion. All 4 decreased RI and PI values compared with their preprocedural values No amenorrhoea or other peri-menopausal symptoms. 2/6 patients had complete loss of ovarian arterial circulation on delayed sonography. 1/2 patients with continued loss of arterial perfusion experienced onset of new menopausal symptoms. Only patient who was >45 years old. 1/2 complete loss of ovarian arterial circulation on sonography resumed normal menses after UAE, no menopausal symptoms at follow up. Ovarian dysfunction was transient in 4/6 patients – see Ryu[70]

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Spies 2001[72] USA Single-centre **Date** Commenced October 1998 **Funding**: Cardiovascular and Interventional Radiology Research and Education Foundation (CIRREF)	**Case series** Prospective **Patients**: 63 **Mean age**: 42.9 (33-50) **Pre UAE** Systematic blood samples FSH levels **Post UAE** 3 and 6 months FSH levels – same laboratory Questionnaire follow up *59 patient at 3 months* *48 patients at 6 months*	**Included** Patients with symptomatic fibroids: heavy menstrual bleeding, pelvic pain or pressure, dyspareunia or urinary or rectal pressure. **Excluded** Menopausal and post menopausal	Bilateral Same physician team **Embolizing material** Polyvinyl alcohol particles (PVA) 500-710 *u*m Gelatin sponge pledgets were not used **Endpoint** Statis or near statis of flow in the uterine arteries	Changes in ovarian function as measured by FSH levels Potentially clinically significant change: >2 SD (7.2 IU/L) increase from baseline Differences by age group. 30-39 years 40-44 45-50 Menopausal symptoms on questionnaire: hot flushes, mood swings, vaginal dryness, post-coital bleeding, weight gain, and bleeding >once every 3 weeks. Statistical significance p.0.05 or less.	**Safety** Fertility Clinically significant changes observed at 3 months in 7 patients. 1/7 <45 years 6/7 45 years and above Progressive increase in FSH levels by age Most patients <45 years no change in ovarian function as measured by basal FSH. Changes >2 SD increase from baseline observed in: 6 patients 45 years and above 1 patient <45 years Patients 45 years and above have a 15% chance of change in FSH levels into peri-menopausal range.

Study	Design/Patients	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Spies 2001[73] USA Single-centre **Date** July 1997 December 1999 **Funding**: Cardiovascular and Interventional Radiology Research and Education Foundation; Boston Scientific; Siemens; Edward Bennett Williams Interventional Radiology Research and Education Fund	**Case series** Prospective Consecutive **Patients**: 200 **Mean age**: 43 (30-52) 45% white : 55% non-white **Post-UAE**: Mean follow up 21 months (minimum 12) Telephone and questionnaire	**Included**: Symptomatic fibroids – predominantly menorrhagia, pressure, pain, bulk-related symptoms **Excluded** Currently pregnant; Infertility attributed to leiomyomas; Desire for future pregnancy if simple myomectomy possible; Pedunculated submucosal fibroids capable of hysteroscopic resection; Uterus size of >24 weeks size.	**Embolizing material**: Polyvinyl alcohol particles (PVA) 500 –710 *u*m Final 100 PVA or tris acryl gelatin microspheres **Endpoint** 1. Slow flow or near-statis in main uterine artery	**Reductions in fibroid and uterine volume** **Changes in symptoms** 11-point scale minus 5 (markedly worse) through 0 to plus 5 (markedly better) **Patient satisfaction** Same scale as for symptoms	**Efficacy** **Symptom improvement** Heavy bleeding 87% 3 months (n=181) 89% 6 months (n=158) 90% 1 year (n=167) Bulk 93% 3 months (n=181) 92% 6 months (n=158) 91% 1 year (n=167) **Satisfaction** 93% 3 months (n=181) 93% 6 months (n=158) 92% 1 year (n=167) (95% response) **Safety** – see Spies[74]

Study	Design/Patients	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Spies 2002[74] USA Single-centre **Date** July 1997 April 2001 **Funding**: None declared	**Case series** Prospective **Patients**: 42/400 **Mean age**: 43 (27-57) 43% white : 57% non-white **Post-UAE**: 24 hours after discharge 1 week clinical visit Questionnaire 3 and 12 months	**Included**: Symptomatic fibroids – predominantly menorrhagia, pressure, pain, bulk-related symptoms **Excluded** Currently pregnant; Infertility attributed to leiomyomas; Desire for future pregnancy if simple myomectomy possible; Pedunculated submucosal fibroids capable of hysteroscopic resection; Uterus size of >24 weeks size.	396 bilateral 4 unilateral **Embolizing material**: First 300 Polyvinyl alcohol particles (PVA) 500 –710 *u*m Final 100 PVA or tris acryl gelatin microspheres **Endpoint** 1. PVA - near-Statis 2. Microspheres - Slow forward flow **Post-op care**: 391/400 hospitalised overnight Discharged next day	**Complications** In-hospital complications similar to FIBROID registry Severity: standard definitions by Society of Cardiovascular and Interventional Radiology (SCVIR). Operative morbidity definitions of the Amercian College of Obstetricians and Gynecologists (ACOG) occurring within 30 days of procedure. Overlapping ACOG criteria counted as one event. Effect on ovarian function	**Safety** – *subset of 250 patients* 3 months 12 months Amenorrhoea 12/250 4/249* (1 lost to follow up*) Ages: 49, 51, 50 and 54. **Complications:** 47 in 42 patients rate10.5% 64% minor (SCVIR classes A and B) – most frequent allergic reaction or rash; 15 major complication on SCVIR classes C and D; 4 Hospitalisation for pain 4 Passage of leiomyoma 2 endometritis 1 Pulmonary embolus 1 Bilateral iliac artery thrombosis 1 uterine infection coinciding with passage of leiomyoma 1 infection – hysteroscopic removal of leiomyoma 1 heavy bleeding during leiomyoma passage – failed D & C subsequent hysterectomy Efficacy data - See Spies[73]

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Tranquart 2002[60] France Single-centre **Date** beginning 1997 **Funding**: None declared	**Case series** Prospective consecutive **Patients**: 58 **Mean age**: 44.5 (33-65) Mean uterus volume 305 (65-1403) cm^3 Mean fibroid volume 112 (10-723) cm^3 **Pre-UAE –** Doppler sonography – same examiner **Post-UAE** Doppler sonography 3, 6, 12 and 24; Clinical examination	**Included:** diagnosis of fibroids confirmed by sonography and gynaecological examination 29 Abnormal bleeding 11 Bulk-related symptoms 5 Pelvic pain 2 Bleeding and pain 8 Bleeding and bulk 2 Bulk and pain 1 Bleeding, bulk and pain 55 Desire to maintain pelvic integrity; 3 Poor operative risk	Inpatient 57 bilateral 1 unilateral **Embolizing materials** 150-250 *u*m polyvinyl alcohol particles and absorbable gelatin sponge **Endpoint** Stagnation of contrast medium in uterine capillary network and absence of uterine flow after contrast injection in hypogastric arteries **Post-op care** Discharged 2 days	Mean reduction in: fibroid and uterine volume; Changes in vascularity Symptom classification (direct questioning) Increased; Unchanged; Improved; Free of symptoms; Patients lost to follow up 58 3 months 46 6 months 36 12 months 19 24 months	**Efficacy** Mean volume reduction n Fibroid % Uterus % 3 month (*58*)* 29 17 1 patient Fibroid volume increased (+42%) 24 months 1 patient free of symptoms new fibroid 1cm^3 3 months 55/58 absence of intrafibroid vessels 21/58 perifibroid vessels persisted No changes in uterine vascularization Symptom change at 3 months: Unchanged 10%; Improved 76% Complete resolution 14% **Safety** 1/46 hysterectomy 1/46 repeat UAE 24 months: 19/19 complete resolution

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Vashisht 2000[24] UK Single-centre **Date** June 1997 January 1999 **Funding**: None declared	**Case series** Prospective **Patients**: 21 **Mean age**: 40 (29-52) **Pre-UAE** MRI **Post-UAE** MRI 2 and 6 months Postal questionnaire 3-12 months (mean 6 months)	**Included:** Diagnosis of fibroids confirmed by MRI Main symptom 13/21 heavy periods 7/21 abdominal distension 1/21 not reported	Not described	Laboratory Median reduction in: fibroid volume; Clinical Menorrhagia Outcomes Questionnaire[81] **Patient satisfaction** Would you recommend UAE to a friend?	**Efficacy** Mean reduction volume (mL) 2 months 6 months % % Fibroid 32.6 75.2 **Mean hospital stay 2.9 days** ***14 patients* (66% response)*** 8/13 Improvement menorrhagia 61% 2/7 Improvement abdominal distension 28.5% 6 Better able – daily activities 2 Better sex life 6 Less tired 7 Better body image 7 Recovery slower than expected **Safety** n=3/21 19**%** 1/21 death septic shock/multiple organ failure 25 days post UAE; 2/21 emergency epidural analgesia; 1/21 readmitted opioid analgesia 6 weeks post UAE **Patient satisfaction*** 7/14 Definitely recommend to friend Results reported for 14 patients

Study	Design/Patients	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Walker 2002[25] UK Single-centre two settings: NHS Trust and private hospital **Date** December 1996 February 2001 **Funding**: None declared	**Case series** Prospective **Patients**: 400 **Mean age**: 43.2 (20-50+) 81% Caucasian 12% Afro-Caribbean 7% Other ethnic origin 4 refused hysterectomy 1 poor operative risk 5 post menopausal 46/400 period-induced anaemia **Pre-UAE** Ultrasound and/or MRI Laboratory tests **During** Radiation exposure **Post UAE** 6 , 12, months ongoing (mean 16.7) Ultrasound and/or MRI Laboratory tests Questionnaires and telephone contacts	**Included**: Gynaecological and radiological evaluation; Symptomatic fibroids either heavy menstrual bleeding or pressure symptoms, abdominal distension, bulk symptoms related to fibroids. Most common symptom abdominal bloating or swelling (98%) Mean 2.4 symptoms per patient Desire to maintain fertility discussed in light of symptoms and surgical options **Excluded** Infertility due to asymptomatic fibroids;	Inpatient 5 Unilateral 395 Bilateral Experienced Interventional Radiologist **Embolizing material** First 66 polyvinyl alcohol particles (PVA) 150-250 and 355-500 *u*m dia. February 1998 thereafter PVA 355-500 *u*m dia. **Endpoint** statis **Post-op care**: Discharge 1-2 days	**Procedure and pain** 3 level classification 1. Better than expected 2. As expected 3. Worse than expected **Severity of pain** 8 point scale from no pain to worse pain ever felt. **Sympton improvement*** 3-point scale: Improvement; Unchanged' Worsened **3 months* **Radiation dose** Fluroscopy time Radiation dose **Process recovery days:** no pain resume usual activities resume work Numbers available to follow up UAE 400 Questionnaire 383 Responders >1 year 262 Responders >2 years 131	**Efficacy** 6-12 months : Volume reduction Uterine Fibroid Mean 55 [SD 18] 73 [SD 25] In 2 patients dominant fibroid volume increased *(latest follow up for each woman)* Symptom improvements 73%-90% 23 treatment failures by 12 months (5 adenomyosis) 3/23 repeat UAE; 9/23 hysterectomies 11/23 other surgical intervention **Safety** 3 Infective complications leading to hysterectomy; 9 Expulsion of fragments two weeks and two years; 5 Hysteroscopic removal of fragments; 13 Vaginal discharge regarded it a major irritant or very troublesome. 26 permanent amenorrhoea Radiation Mean fluoroscopy time 25.9 minutes and 44.6 minutes in women treated in one or two procedures respectively. Mean radiation dose 7954.4 and 14631.3 cGy cm^2 Fluoroscopy time statistically correlated with experience of interventional radiologist **Patient satisfaction** *latest follow up for each woman* 97% satisfied with procedure and outcome; 97% would recommend UAE to others

Study	Design/Patients/Participants	Inclusion/Exclusion	Procedure/materials	Outcome measures	Results
Zupi 2003[61] Italy Single-centre **Date** April 1999 February 2000 **Funding**: None declared	**Case series** Prospective **Patients**: 26 **Mean age**: 39.5 (32-54) Mean fibroid size 276.8 ± 241.2 (range 40.3 mL and 363.5 mL) **Pre-UAE –** Trans abdominal and transvaginal Doppler sonography **Post-UAE** Doppler sonography 1, 3 and 6 months MRI 12 months	**Included:** Single myoma or large myoma; Intramural location; Fertile age. Menorrhagia, pelvic pain and abdominal mass	Inpatient 26 bilateral 355-500 *u*m dia. polyvinyl alcohol particles	Mean reduction in: uterine volume Symptom changes over time; Vascularization high, moderate, low. **Radiation**: Fluoroscopic time Ovarian dose Skin dose	**Efficacy** Mean reduction uterine volume 6 month 64% 12 months 83% Most reduction in fibroids with high vascularity Mean recovery 2.3 days Total regression of symptoms % 12/21 Menorrhagia 57 7/9 Pain 77 8/12 Urinary disturbance 66 18/18 Abdominal weight 100 **Safety** **%** 26 Pain 100 19 Fever 24–72 hours 73 15 Nausea 58 2 Expelled myoma debris 4 weeks post-UAE 8 Radiation Mean fluoroscopic time 20 minutes Ovarian dose 3.76-55.82 cGy(18.75 ± 13.78 cGy) Skin dose 54.66-767.11 cGy(126.71 ± 71.17 cGy) Other issues: experience of operator