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Uterine-Preserving Interventions for the Management of Symptomatic Uterine Fibroids: A Systematic Review of Clinical and Cost-Effectiveness

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CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Acronyms and Abbreviations

CRD	Centre for Reviews and Dissemination
DDI	Defecation Distress Inventory
EMMY	the EMbolization versus hysterectoMY study
EQ-5D	EuroQol 5–Dimensions Questionnaire
GnRH	gonadotropin-releasing hormone agonist
HOPEFUL	Hysterectomy Or Percutaneous Embolisation for Uterine Leiomyomata study
HRQoL	health-related quality of life
HUI-3	Health Utilities Index Mark 3
IIQ	Incontinence Impact Questionnaire
MRgFU	magnetic resonance-guided focused ultrasound
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RFVTA	radiofrequency volumetric thermal ablation
RCT	randomized controlled trial
RR	relative risk
SF-36	Short Form (36) Health Survey
SOGC	Society of Obstetricians and Gynaecologists of Canada
UAE	uterine artery embolization
UAO	uterine artery occlusion
UFQoL	Uterine Fibroid Quality of Life Questionnaire
UFS-QOL	Uterine Fibroid Symptom and Quality of Life Questionnaire

Executive Summary

Context and Policy Issues

Uterine fibroids are the most common pelvic tumours and the most common benign tumours in women. Usually diagnosed late in a woman's reproductive life, fibroids are present in up to 40% of women older than 40 years. Fibroid-related symptoms are often divided into menstrual symptoms, such as heavy bleeding, or bulk-related symptoms that result from the enlargement of the uterus. Common symptoms include abnormal uterine bleeding, pelvic pressure and pain, infertility, recurrent pregnancy loss, and decreased quality of life. Medications or surgical interventions may be needed to treat fibroids. Hysterectomy is a definitive solution for many women; however, alternatives that preserve fertility and avoid invasive surgery do exist. The less-invasive uterine-preserving alternatives include myomectomy, uterine artery embolization or occlusion (UAE or UAO), myolysis, and endometrial ablation. Each carries its own safety and effectiveness profile, and the treatment of fibroids must be individualized depending on such factors as symptoms, size and location of fibroids, age, desire for future pregnancy or preservation of the uterus, the availability of therapy, physician experience, and patient preference.

To help guide decisions about the treatment of fibroids, this study systematically reviews the clinical and cost-effectiveness of interventions for symptomatic uterine fibroids that preserve the uterus and are available in Canada, compared with each other or with hysterectomy. Medications have been excluded from this comparison, but do provide an alternative option for short-term therapy.

Research Questions

1. What is the clinical effectiveness and safety of uterine-preserving interventions for the treatment of symptomatic uterine fibroids, compared with each other or with conventional treatment (hysterectomy)?
2. What is the cost-effectiveness of uterine-preserving interventions for the treatment of symptomatic uterine fibroids, compared with each other or with conventional treatment (hysterectomy)?

Methods

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, The Cochrane Library, and the University of York Centre for Reviews and Dissemination (CRD) databases. Grey literature was also searched. The search for health technology assessments, systematic reviews, meta-analyses, and guidelines was limited to documents published since January 1, 2005, while the search for randomized controlled trials (RCTs), controlled clinical trials, cohort studies, and economic studies was not limited by publication year. Regular alerts were established to update all searches until project completion. Predefined eligibility criteria included RCTs, non-randomized studies, and economic evaluations assessing the clinical, cost-effectiveness and safety of uterine-preserving interventions in women with symptomatic uterine fibroids. The interventions of interest included myomectomy, myolysis, UAE, UAO, or endometrial ablation. They were compared with each other or with hysterectomy.

Two reviewers independently selected studies. A data extraction form for the clinical effectiveness review was designed a priori to document and tabulate

relevant study characteristics. Data were extracted by one reviewer, and were verified by the second reviewer for accuracy and completeness. The Downs and Black checklist and the Drummond checklist were used to assess the quality of the included clinical studies and economic evaluations, respectively. Any disagreements were resolved through discussion until consensus was reached. Meta-analyses and subgroup analyses were not possible. A narrative synthesis of results of included studies was conducted.

Summary of Findings

Ten RCTs and 16 non-randomized studies were included for the clinical review. The uterine-preserving interventions examined were myomectomy, UAE, UAO, magnetic resonance-guided focused ultrasound (MRgFU), and radiofrequency volumetric thermal ablation (RFVTA). In general, the quality of these studies was low due to small sample sizes and imbalanced baseline patient characteristics between groups, particularly in non-randomized controlled trials. Inconsistent results were observed across the included studies. In addition, the amount of available evidence is limited, and some of the recruited patients may not be suitable candidates for a particular treatment, which limits the applicability of the evidence across treatments.

In summary:

- UAE, myomectomy, UAO, RFVTA, and MRgFU reduced fibroid-related symptoms and enhanced patient quality of life from baseline.
- UAE was superior to myomectomy in reducing abnormal uterine bleeding. Compared with myomectomy and hysterectomy, UAE had a lower risk of peri-procedural complications, shorter hospital stay, and higher patient satisfaction. However, it was associated with a higher risk of re-intervention compared with UAO.
- Myomectomy was superior to UAE in improving bulk symptoms. It also had better pregnancy outcomes, based on limited clinical evidence.
- UAO was associated with a lower risk of complications compared with UAE.
- RFVTA had a lower risk of peri-procedural complications, had shorter hospital stay, and was associated with more re-interventions in the future, compared with myomectomy.
- MRgFU was associated with fewer complications but more re-interventions, compared with UAE and hysterectomy.

In the economic review, the cost-effectiveness of UAE, MRgFU, myomectomy, hysterectomy, and pharmacotherapy was examined in seven economic evaluations performed in North America (one in Canada) and Europe. None of the identified economic evaluations considered all treatments in a single analysis. Findings from the Canadian economic evaluation suggest that when 35% of patients were assumed eligible for treatment with MRgFU, UAE was more cost-effective than MRgFU, hysterectomy, and myomectomy at commonly accepted willingness-to-pay thresholds. Compared with hysterectomy, UAE had an incremental cost-effectiveness ratio of $46,480 per quality-adjusted life-year gained.

Conclusions and Implications for Decision- or Policy-Making

Evidence from 26 studies on the clinical effectiveness and safety of uterine-preserving interventions to manage symptomatic uterine fibroids was reviewed. Study findings suggested that UAE, RFVTA, and MRgFU were associated with fewer procedure-related complications, shorter hospital stay, and higher patient satisfaction, compared with hysterectomy, in short-term follow-up; however,

patients treated with hysterectomy reported better health-related quality of life. In the long term, uterine-preserving interventions are linked to more re-interventions. Patients treated with myomectomy had better reproductive outcomes than UAE, based on limited clinical evidence.

While results from the economic literature vary, given differences in settings, populations, and perspectives, there is one Canadian economic evaluation that suggests that when 35% of patients are assumed eligible for treatment with MRgFU, UAE is more cost-effective than MRgFU, hysterectomy, and myomectomy.

Context and Policy Issues

Uterine fibroids (or leiomyoma) are the most common pelvic tumours and the most common benign tumours in women. Why fibroids develop and grow is not fully understood, but hormones play a role.[1] Age is a risk factor for their development. Uterine fibroids are usually diagnosed late in a woman's reproductive life and are present in up to 40% of women older than 40 years. The prevalence of fibroids increases with age until menopause. Ethnicity is another risk factor for uterine fibroids. African-American women have a higher incidence of fibroids — 60% by age 35 and more than 80% by age 50, compared with Caucasian women, whose incidence of fibroids is 40% by age 35 and almost 70% by age 50.[2]

Approximately 20% to 50% of fibroids are symptomatic.[3] Symptoms may include abnormal uterine bleeding, pelvic pressure and pain, infertility, and recurrent pregnancy loss. As a result, uterine fibroids may lead to a significant reduction in a woman's quality of life.[1,4,5]

Asymptomatic fibroids may be discovered on routine pelvic examination and are verified with an ultrasound. According to clinical practice guidelines developed by the Society of Obstetricians and Gynaecologists of Canada (SOGC) in 2015, treatment of fibroids must be individualized and the following factors should be considered: symptomatology, size and location of fibroids, age, desire for future pregnancy or preservation of the uterus, the availability of therapy, and the experience of the therapist.[3] For example, magnetic resonance-guided focused ultrasound (MRgFU) is appropriate only for single fibroids in an individual session, uterine artery embolization (UAE) is contraindicated in submucosal fibroids, and likewise laparoscopic radiofrequency volumetric thermal ablation (RFVTA) is not indicated for submucosal fibroids, although hysteroscopic RFVTA can be used in this circumstance.[3]

Removal of the uterus (hysterectomy) can be a definitive solution for many women with fibroids. In Canada, approximately 30% of the hysterectomies performed are for uterine fibroids,[6] and a similar percentage (33%) was reported for fibroid treatment in a British study.[2] However, alternatives to hysterectomy that preserve fertility and potentially avoid invasive surgery are of interest to patients and health care professionals. Alternatives include myomectomy (surgical removal of the fibroid), UAE or uterine artery occlusion (UAO) (disruption of the blood supply to the fibroid with small particles, or via laparoscopically or transvaginally placed vascular clamp), myolysis (destruction of the fibroid or disruption of the blood supply within the fibroid with targeted energy such as radiofrequency electricity, laser energy, or focused ultrasound), and endometrial ablation (destruction of the uterine lining using various

modalities such as thermal balloon, radiofrequency mesh electrode, or microwave energy).[3,5,7] Compared with hysterectomy, these interventions are less invasive and the uterus is preserved. Each technology carries a specific safety and effectiveness profile; therefore, the best candidates for one option may not be the best candidates for another. In addition, the technologies all vary significantly in cost. Not all technologies are readily available across Canada, such as MRgFU, and this lack of accessibility may limit their use. The choice of intervention is also influenced by patient preference.

Drug therapy with selective progesterone receptor modulators or gonadotropin-releasing hormone (GnRH) agonists has also been shown to reduce fibroid-related abnormal uterine bleeding and bulk symptoms such as pelvic pressure. However, at present in Canada, the only indicated medication for the management of symptomatic uterine fibroids is a three-month course of ulipristal acetate.[3,6,8]

This study systematically reviews the clinical and cost-effectiveness of non-pharmacological interventions for symptomatic uterine fibroids that preserve the uterus and are available in Canada, compared with each other or with conventional surgical treatment (hysterectomy) to help to identify the optimal fibroid management options for clinical practice. The optimal strategy may differ depending on the patient or the characteristics of the fibroid, and these differences will be considered in the review by using subgroup analysis when data are available. Pharmacotherapy has been excluded from this comparison, but is a viable alternative for short-term therapy at present.

Research Questions

1. What is the clinical effectiveness and safety of uterine-preserving interventions for the treatment of symptomatic uterine fibroids compared with each other or with conventional treatment (hysterectomy)?
2. What is the cost-effectiveness of uterine-preserving interventions for the treatment of symptomatic uterine fibroids compared with each other or with conventional treatment (hysterectomy)?

Key Findings

Following treatment with uterine-preserving interventions (UAE, UAO, myomectomy, RFVTA, or MRgFU) for symptomatic uterine fibroids, symptoms of abnormal uterine bleeding and pelvic pressure were reduced from baseline. Compared with conventional hysterectomy, uterine-preserving interventions are associated with fewer complications, shorter hospital stay, and higher patient satisfaction; however, patients treated with hysterectomy reported better health-related quality of life. The quality of the included studies was lower due to small sample sizes and study design. Data on reproductive outcomes were reported, but should be interpreted with caution, because a statistically significant difference may not be detectable in a small study population.

Findings from a Canadian economic evaluation indicated that when 35% of patients were assumed eligible for the treatment with MRgFU (a commonly accepted value in economic models evaluating MRgFU), UAE was more cost-effective than focused ultrasound, hysterectomy, and myomectomy.

Pharmacotherapy was not included in this comparison and may be an option in the future if long-term treatment becomes available.

Methods

Literature Search Strategy

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, The Cochrane Library, and the University of York Centre for Reviews and Dissemination (CRD) databases. Grey literature (literature that is not commercially published) was identified by searching relevant sections of the *Grey Matters* checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine). Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, cohort studies, case-control studies, and economic studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English- or French-language documents. Conference abstracts were excluded from the search results. The search for RCTs, controlled clinical trials, cohort studies, and economic studies was not limited by publication year. The search for health technology assessments, systematic reviews, meta-analyses, and guidelines was limited to documents published since January 1, 2005. Regular alerts were established to update all searches until project completion. The search strategy is presented in Appendix 1.

Selection Criteria and Methods

Two reviewers independently screened the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria, ordered the full text of any articles that appeared to meet those criteria. The reviewers then independently reviewed the selected full-text articles, applied the selection criteria, and compared the independently chosen included and excluded studies. Disagreements were resolved through discussion until consensus was reached. Duplicate publications of the same trial were excluded unless they provided additional outcome information of interest.

Table 1: Selection Criteria

Population	Women with symptomatic uterine fibroids **Possible subgroups:** • Age • Size of uterus or fibroid(s), number of fibroids, location of fibroids • Types of symptoms (e.g., heavy menstrual bleeding, pain, pressure) • Previous treatment for uterine fibroids • Anemia • Body mass index
Intervention	**Uterine-preserving interventions to eliminate or specifically alleviate fibroid-related health problems:** • Myomectomy (laparotomy, laparoscopy, or hysteroscopy) • Myolysis (focused ultrasound, laser, radiofrequency, or other methods) • Uterine artery embolization • Endometrial ablation (electrosurgery, heat, laser, radiofrequency, or other methods) • Uterine artery occlusion or ligation
Comparator	• Other uterine-preserving interventions, such as those previously listed • Watchful waiting and/or monitoring • Placebo or sham interventions • Drug therapy (selective progesterone receptor modulators, gonadotropin-releasing

	hormone analogues) • Hysterectomy
Outcomes	**Clinical effectiveness:** • Change in abnormal uterine bleeding • Change in pelvic pressure (pain, bladder pressure, painful sexual intercourse, urinary frequency, incontinence, nocturia, or constipation) • Change in fibroid size • Health-related quality of life • Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery) • Relapse or re-intervention rate • Length of hospital stay • Patient satisfaction **Cost-effectiveness:** • Incremental cost-effectiveness ratio • Quality-adjusted life-year • Incremental net monetary benefit • Incremental net health benefit **Safety:** • Adverse events (such as operation complications, pregnancy complications)
Study Designs	• Randomized controlled trials and non-randomized studies with a control group • Economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, or if they were duplicate publications of the same study. Studies of infertile women who are asymptomatic were excluded. Studies evaluating the effectiveness of combination therapy were excluded. Economic studies were excluded if they reported cost data only. Exclusion of economic studies conducted in countries with a health care system greatly different from Canada, due to the challenge in generalizing the study results to the Canadian context.

Data Extraction Strategy

A data extraction form for the clinical effectiveness review was designed a priori to document and tabulate relevant study characteristics. Data were extracted by one reviewer, and were verified by the second reviewer for accuracy and completeness. Any disagreements were resolved through discussion until consensus was reached.

Critical Appraisal of Individual Studies

The validated Downs and Black checklist[9] was used to assess the study quality of RCTs and non-randomized studies based on the quality of reporting, external validity, and risk of bias. The quality of the economic evaluations was assessed using the Drummond checklist.[10] Numeric scores were not calculated; rather, the strengths and limitations of the included studies were described narratively.

Data Analysis Methods

Meta-analyses were not possible due to the variability in study characteristics, such as the instruments used for symptom assessment, and outcome measures with diverse definitions. Instead, a narrative synthesis and summary of findings

were presented. In the included clinical studies, there were no data on any of the predefined subgroups; therefore, subgroup analyses were not performed.

Results

Quantity of Research Available

The process of study selection is outlined in the PRISMA flowchart (Appendix 2). The literature search yielded 1,189 citations. Upon screening titles and abstracts, 1,055 citations were excluded and 134 potentially relevant articles were retrieved for full-text review. Four potentially relevant reports were retrieved from grey literature, handsearching, and literature alerts.[11] Of the 138 potentially relevant reports, 43 were selected as being relevant to the research questions and 95 were excluded. Of the 43 reports, 35 (on 26 unique studies) addressed the clinical research questions with respect to the clinical effectiveness and safety of uterine-preserving interventions, and eight (on seven unique studies) addressed the economic research questions about the cost-effectiveness of these interventions.

Included clinical studies are listed in Appendix 3, while articles that did not meet the inclusion criteria for this review are listed in Appendix 4.

Clinical Review

Study Characteristics

This systematic review identified 26 unique clinical studies (reported in 35 publications) assessing the treatment effects of various uterine-preserving interventions in women with symptomatic uterine fibroids. These interventions were compared either with the conventional surgical intervention (hysterectomy), or with other uterine-preserving interventions. The interventions included in this review are myomectomy, UAE, UAO, MRgFU, and RFVTA. The following comparisons were identified from the literature:

- UAE versus hysterectomy versus myomectomy: one non-randomized study[12] (this study had three active treatment arms. Results of these comparisons are reported in their respective categories: UAE versus hysterectomy, UAE versus myomectomy, and hysterectomy versus myomectomy)
- Myomectomy versus hysterectomy: three non-randomized studies[13-15]
- UAE versus hysterectomy: three RCTs[16-18] and three non-randomized studies[19-21]
- UAE versus myomectomy: two RCTs[22,23] and five non-randomized studies[24-28]
- UAE versus UAO: four RCTs[29-32] and two non-randomized studies[33,34]
- UAE versus MRgFU: one non-randomized study[35]
- MRgFU versus hysterectomy: one non-randomized study[36]
- Myomectomy versus RFVTA: one RCT.[37]

Individual clinical study details are presented in Tables 5-1 to 5-8 in Appendix 5.

UAE Versus Hysterectomy Versus Myomectomy

In one American study enrolling 375 patients,[12] the clinical effect of UAE, hysterectomy and myomectomy on health-related quality of life (measured with generic and disease-specific quality of life assessment tools) were compared to each other as well as with controls with no history of uterine fibroid who had regular menstrual cycles. Results from this study (UAE versus hysterectomy; myomectomy versus hysterectomy; UAE versus myomectomy) are presented under the respective comparisons.

Myomectomy Versus Hysterectomy

The four non-RCTs included one three-arm prospective cohort study[12] and three retrospective cohort studies,[13-15] with the span of publication dates ranging from 1996 to 2015. Three were conducted in the United States[12,14,15] and one in the United Kingdom.[13] The number of study participants ranged from 167 to 400 across the studies. Patient baseline characteristics varied between the comparison groups. Compared with women in the myomectomy group, those in the hysterectomy group were older, had larger uterus size, complained about abnormal uterine bleeding more often and had more previous pregnancies. In the prospective study, different types of hysterectomy and myomectomy were performed abdominally or vaginally via open surgery or endoscopy. Hysterectomy and myomectomy were performed abdominally in the retrospective studies. The key outcome measures were health-related quality of life (measured with generic and disease-specific quality of life assessment tools) in the prospective study and peri-operative complications such as fever and need for blood transfusion in the three retrospective studies.

UAE Versus Hysterectomy

The seven studies included in this category were conducted in Europe[16-20] and the United States.[12,21] The number of study participants ranged from 40 to 1,108 across the studies. Two of the studies reported long-term outcomes: the EMbolization versus hysterectoMY (EMMY) study[17] presented data up to five years after the primary intervention, while patients in the Hysterectomy Or Percutaneous Embolisation for Uterine Leiomyomata (HOPEFUL) study[20] were followed over five years. More than 1,000 patients were recruited in the HOPEFUL study; however, subgroup analysis was not conducted, due to the insufficient power in the small subgroups if data were analyzed separately. Various routes of access were used in hysterectomy, but in the majority of cases, this surgery was performed abdominally. In the RCTs,[16-18] patients' baseline characteristics were comparable between treatment groups with respect to age, fibroid size, presenting symptoms, and previous fibroid therapy. Intramural fibroids were commonly presented in both groups. In the non-RCTs (three prospective studies[12,19,21] and one retrospective study[20]), patients in the two treatment groups had similar age and uterus and fibroid size, but the hysterectomy patients had higher previous pregnancy rate than the UAE patients. Improvement in fibroid-related symptoms and change in health-related quality of life were the main outcome measures in these studies.

UAE Versus Myomectomy

Of the eight studies identified for this comparison, two were RCTs[22,23] and six were prospective[12,25,26] or retrospective[24,27,28] cohort studies. They were conducted in Europe[22,23] or the United States.[12,24-28] The number of study participants ranged from 81 to 375 across the studies. Myomectomy was performed via different routes: open abdominal myomectomies were performed in six studies,[22,24-28] open or laparoscopic myomectomies were performed in one study,[23] and one study did not provide the details of myomectomy.[12] Patients' baseline characteristics were generally imbalanced between the two treatment groups in the non-randomized studies. Women who had UAE tended to be older[12,24-28] and had larger uteri,[12,25,26] and abnormal uterine bleeding was usually the main complaint in this group.[22,24-27] Patients who had myomectomy were more likely to report pelvic pressure symptoms.[26-28] Improvement in fibroid-related symptoms and change in health-related quality of life (measured with generic and disease-specific quality of life assessment tools) were the main outcome measures in these studies.

UAE Versus UAO

Six studies (four RCTs[29-32] and two prospective cohort studies[33,34]) were included for this comparison. They were conducted in Egypt,[29] India,[30] the United States,[31] and Europe.[32-34] The number of participants in the four RCTs ranged from 14 to 90. Comparisons of patient baseline characteristics between UAE and UAO were inconclusive, due to the small patient population. In one non-randomized study that enrolled 200 participants,[33] patients treated with UAE had larger fibroid size than those treated with UAO at baseline (68.2 mm in diameter versus 48.3 mm, respectively). In the second non-randomized study, pregnancy outcomes were reported in 34 patients.[34] Data in this study were inadequately reported; therefore it was difficult to examine the study characteristics and the baseline patient characteristics.[34] Improvement in menstrual blood loss and post-procedural complications were the main outcome measures in these studies.

UAE Versus MRgFU

In one prospective cohort study,[35] the effect of UAE on fibroid-related symptom relief was compared with MRgFU in 119 Dutch women with symptomatic fibroids.

Patients treated with MRgFU were older, had larger fibroids, and were more likely to complain about bulky symptoms such as pelvic pain, while heavy uterine bleeding was more common in the UAE group.

MRgFU Versus Hysterectomy

One multi-country prospective study[36] compared the effectiveness and safety of MRgFU with total abdominal hysterectomy. Premenopausal women who did not desire pregnancy in the future were recruited simultaneously for the treatment with MRgFU (n = 109) or hysterectomy (n = 83). MRgFU was allowed in women with multiple fibroids. Compared with the MRgFU group, patients in the hysterectomy group had higher body mass index (BMI), more severe fibroid-related symptoms, and poorer health-related quality of life at baseline. The patients who underwent hysterectomy took more medication for fibroids before entering the study.

Myomectomy Versus RFVTA

One RCT[37] evaluated the treatment effect of myomectomy relative to RFVTA on fibroid-related symptom relief and procedure-related complications in 50 German patients. Both myomectomy and RFVTA were performed via laparoscopy. Compared with the myomectomy group, patients in the RFVTA group were older and had more complaints about heavy menstrual bleeding but less pelvic discomfort and pain. Intramural and subserosal fibroids accounted for more than 95% of the total number of treated fibroids.

No evidence was found on the treatment effect of endometrial ablation, which was identified as an intervention of interest in the research protocol.

Critical Appraisal of Individual Studies

The objectives were clearly described in all included studies. Conflict of interest and funding source were declared in the majority of the studies.[12,13,16,17,19-23,25,26,28,31,33,35,37] A description of the intervention under investigation was provided in all RCTs. Interventions were insufficiently described in three non-RCTs.[12,34,36]

Of the 26 clinical studies, 16 were non-RCTs.[12-15,19-21,24-28,33-36] Patients in each treatment group were recruited over the same period of time in seven studies.[19,25-28,33,36] It was unclear whether the patients were recruited over the same period of time in seven studies.[12-14,21,24,34,35] In two studies, participants were enrolled at different periods of time.[15,20] If patients are not enrolled and treated over similar time periods in each group, it is possible that any differences seen are due to other changes between time periods (such as changes in standard of care or hospital practices) and not necessarily wholly due to the intervention itself. The treatment plan in these studies was developed according to the patient's health status, severity of disease, reproductive history, standard of care in the specific study site, or patient preference. In general, patient baseline characteristics (such as age; parity; size, number, and location of the fibroids; severity of symptoms; and previous fibroid management) in these non-RCTs were not comparable between the comparison groups. For instance, when comparing myomectomy with hysterectomy, women in the myomectomy group tended to be younger and had fewer previous pregnancies; however, patients who had had hysterectomy were older and had larger uterine fibroids, and menorrhagia was more common in this group. The interpretation of the study findings is challenging when patient baseline characteristics are imbalanced between

treatment groups, because the treatment decisions were influenced by a variety of factors such as participants' clinical characteristics, desire for future pregnancy, preference, availability of a certain intervention, or the clinician's experience. For instance, women with larger fibroids may suffer from more severe symptoms and request more aggressive treatment (such as hysterectomy), and report better quality of life after the intervention, while women with smaller fibroids may prefer myomectomy to preserve the uterus; however, the regrowth of the fibroids can lead to further treatment in the future and negatively affect their quality of life. In addition, while the inclusion of a control group may increase the strength of the conclusions, these observational studies suffer from a risk of bias due to confounding by indication and uncontrolled confounders. Even though some non-RCTs indicated that potential confounders had been identified a priori and appropriate statistical methods were employed to adjust for the confounding effects,[14,20,21,21,24,35] it is unclear whether all the relevant confounders have been recognized. It is challenging to draw conclusions based on these imbalanced baseline characteristics and uncertainty.

Many of the included studies recruited a small number of patients. A description of the sample size calculation or power calculation was often absent from the published reports, especially for non-randomized studies. Therefore, it is questionable as to whether these studies have sufficient power to detect clinically and statistically meaningful differences (if they exist) between the treatment groups for all outcomes of interest.

All but two[31,37] of the included RCTs were open label, due to the nature of the procedures. This could have an impact on patient-reported outcomes such as health-related quality of life, change in symptoms, or treatment-related adverse events. Some RCTs indicated that patients were informed of the benefits and risks of both treatment options prior to the procedure,[29,31,32] but it was unclear whether patients in other RCTs had knowledge of the assigned treatment. Randomization was carried out using computer-generated random number in most of the RCTs, except for three studies comparing UAE with UAO or hysterectomy,[16,29,31] where sealed envelopes were used in treatment assignment but no further details were provided to determine the appropriateness of the randomization process. Loss of follow-up was reported in the majority of the studies, except for one RCT[30] and seven non-RCTs.[13,14,21,27,28,34,36] The rates of loss of follow-up were low (< 5%) and equally balanced across the treatment groups in most of the studies; however, high rates were observed in some studies: 15% for UAE versus 19% for myomectomy,[22] 8% for UAE versus 13% for hysterectomy (at two-year follow-up),[20] 17% for UAE versus 10% for myomectomy versus 14% for hysterectomy,[12] and 18% for MRgFU versus 22% for UAE.[35] This may be a concern in the interpretation of results, especially for studies with small sample size. In one RCT that enrolled 14 patients, three patients (38%) and one patient (17%) were lost to follow-up from the UAE group and the UAO group, respectively.[31] Methods of missing data imputation were described in two studies.[20,24]

With respect to the external validity of the clinical evidence, some studies were published in the 1990s, when the technologies, equipment, and practice patterns were likely different from the current practice.[2] In addition, due to the inadequate reporting of the patient and disease characteristics, it was often not clear whether the populations studied reflected the larger populations from which they were drawn and to whom study results are intended to apply.

A summary of the strengths and limitations of the individual studies is presented in Appendix 6.

Data Analyses and Synthesis

Findings from the individual studies are presented in Appendix 7. Meta-analyses and subgroup analyses were not possible due to the variability in study characteristics, such as the instruments used for symptom assessment, and outcome measures with diverse definitions.

Myomectomy Versus Hysterectomy

Change in Symptoms / Health-Related Quality of Life

One non-RCT[12] reported changes in symptom severity and health-related quality of life. The results suggested that one year after the procedure, compared with myomectomy, patients treated with hysterectomy reported statistically significant improvement in the Symptom Severity subscale and the health-related quality of life (HRQoL) subscale of the Uterine Fibroid Symptom and Quality of Life Questionnaire (UFS-QOL) ($P < 0.01$).

Complications

Four studies reported on this outcome.[12-15] Conflicting results were found across the studies for blood loss: in one study published in 2005,[13] laparoscopic hysterectomy was associated with significantly less blood loss during the procedure than laparoscopic myomectomy (215.1 mL versus 316.2 mL, $P < 0.0001$). However, in another study published in 2000,[14] abdominal (laparotomy) hysterectomy was related to statistically significantly more blood loss than abdominal myomectomy (483.6 mL versus 226.7 mL, $P = 0.00001$). In the study of laparoscopy procedures, bladder injury was reported in three patients (1.6%) who underwent hysterectomy, but none was reported in the myomectomy group.[13] Four patients (1.9%) in the laparoscopic myomectomy group converted to laparotomy during the surgery, while no patient in the laparoscopic hysterectomy needed the conversion.[13] The results indicated that open abdominal hysterectomy was related to more peri-procedural complications (blood loss and organ injury), compared with the abdominal myomectomy. On the other hand, laparoscopic myomectomy was related to fewer organ injuries but higher risk of converting to the open surgery, compared with the laparoscopic hysterectomy. Different routes of hysterectomy or myomectomy had an impact on the procedure-related complications.

Length of Hospital Stay

Three studies reported on this outcome.[12-14] Inconsistent results were reported: hysterectomy was related to shorter hospital stay than myomectomy in two studies (1.81 days versus 2.12 days in a 2015 study of laparoscopic procedures, $P = 0.0003$;[13] 1.9 days versus 2.1 days in a 2010 study [route of procedure was not specified], P value was not reported[12]), but related to longer hospital stay in the third (4.42 days versus 3.96 days in a 2000 study of open abdominal procedures, $P = 0.048$).[14] The results indicated that an abdominal hysterectomy was related to longer hospital stay than an abdominal myomectomy, while a laparoscopic hysterectomy was related to shorter hospital stay than a laparoscopic myomectomy. Although statistically significant differences were observed between treatment groups for the length of hospital stay, the differences may not be considered clinically important.

UAE Versus Hysterectomy

Change in Symptoms

Six studies reported on this outcome.[12,16,18,20,21,38] Findings from one RCT with six-month data suggested that improved menstrual bleeding occurred in 86% of the patients (cessation of heavy menstrual bleeding in 56% of patients, reduction in blood volumes in 14%, and amenorrhea in 17%) in the UAE group.[18] Two other RCTs[16,39] indicated that two years after UAE, approximately two-thirds of the patients (62% to 67%) reported substantial improvement in heavy menstrual bleeding. No information was provided for the scales that were used in bleeding assessment. Five years after UAE, 76% of the women who had an intact uterus were no longer experiencing menorrhagia. Data from one non-RCT[21] up to one year post-procedure supported the results from the RCTs, showing similar improvement in bleeding in women who underwent UAE. In addition, UAE and hysterectomy both eased pelvic pressure. The between-group difference was statistically significant in one RCT[16] ($P = 0.029$). At baseline, 74% of the UAE patients reported pelvic pressure symptoms, with 95% of those individuals reporting symptom relief at year 2 follow-up, compared with 87% of the hysterectomy patients reporting pelvic symptoms at baseline and 69% of them reporting symptom relief at year-2 follow-up), but not in another[38] ($P = 0.71$). Similar percentages of patients reported pelvic symptoms at baseline between treatment groups.

Health-Related Quality of Life

Three studies reported on this outcome.[12,21,38] Various instruments were used to examine patients' general health status and disease-specific quality of life. Two-year and five-year data in the EMMY study[17,40] indicated that there were no statistically significant differences between UAE and hysterectomy in improving quality of life outcomes measured by generic questionnaires such as the Short Form (36) Healthy Survey (SF-36), the Health Utilities Index Mark 3 (HUI-3), the EuroQol 5–Dimensions Questionnaire (EQ-5D), and disease-specific instruments such as the Defecation Distress Inventory (DDI) and Incontinence Impact Questionnaire (IIQ), although these scores were improved significantly from baseline in both groups ($P < 0.05$), except for the DDI score, in that the improvement from baseline was observed only in patients who underwent UAE, but not in those who underwent hysterectomy. Data from one non-RCT[12] suggested that treatment with hysterectomy was associated with significantly greater improvement in the HRQoL total score in UFS-QOL.

Complications

Six studies reported on this outcome.[12,16,18,20,21,38] The risk of peri-operative complication was lower in the UAE group, where patients had statistically and clinically significantly less blood loss (436.1 mL with hysterectomy versus 30.9 mL with UAE) and reported less severe pain compared with those in the hysterectomy group.

Re-intervention

Six studies reported on this outcome.[12,16,18-20,38] There was no statistically significant difference in the need for further interventions between the two groups, according to the data up to five years.

Patient Satisfaction

Six studies reported on this outcome.[16,18-21,38] Findings from RCTs and non-randomized studies suggested that the vast majority of the patients were satisfied with the treatment

they were assigned. Mixed results were reported and the between-group differences were statistically significant in some studies.[20,38]

Length of Hospital Stay

Five studies reported on this outcome.[12,18,19,21,38] Abdominal hysterectomy was performed in three studies;[17-19] laparoscopic, abdominal, or a combination of laparoscopic and vaginal hysterectomy was performed in one study;[21] and the route of hysterectomy was not specified in one study.[12] Treatment with UAE was related to shorter hospital stay compared with hysterectomy ($P < 0.001$ was reported in one RCT[18] and one non-randomized study;[21] *P* values were not reported in the other studies, but a similar trend was observed for length of hospital stay in the comparison between UAE and hysterectomy).

UAE Versus Myomectomy

Change in Symptoms

Seven studies reported on this outcome.[22-28] Symptom relief from baseline was observed in both UAE and myomectomy groups one year after the procedure. Statistically significant between-group differences in improving symptoms of bleeding (favouring UAE) and pelvic pressure (favouring myomectomy) were reported in one non-RCT, when patients were followed approximately 14 months after the primary procedure.[27] Improvement in fibroid-related symptoms from baseline was also observed in both treatment groups in the other six studies; however, the between-group differences were either not statistically significant, or a *P* value for the statistical comparison was not reported.

Health-Related Quality of Life

Four studies reported on this outcome.[12,22,25,26] Patients' quality of life improved significantly from baseline in both groups, measured with SF-36, UFS-QOL, and the Uterine Fibroid Quality of Life questionnaire (UFQoL). At the end of the studies (up to one-year follow-up), a statistically significant difference was not detected between UAE and myomectomy, except that in one non-RCT, more patients in the UAE group showed at least a 5-point increase in the UFQoL questionnaire (a 5-point increase in UFQoL indicates successful treatment and was considered clinically meaningful in this study) than the myomectomy group.[26]

Complications

Seven studies reported on this outcome.[12,22-27] Higher risks of procedure-related complications were observed in patients in the myomectomy group than in the UAE group. Common procedure-related complications included injury of organs in the abdominal cavity, unplanned conversion from laparoscopic myomectomy to open surgery, infection, excessive pain, blood loss, or transfusion. The between-group difference was considered statistically significant in some studies (all were non-randomized studies),[24-27] but not all.

Reproductive Outcomes

Three studies reported on this outcome.[23,25,26] The Mara 2008 study[23] enrolled patients who planned pregnancy. In this study, among the patients who tried to conceive, those in the myomectomy group had higher pregnancy rate and higher delivery rate, compared with the UAE group. No pregnancy was observed at year 1 follow-up in one non-RCT,[25] and two unplanned pregnancies were reported in the UAE group at year 2 follow-up in another study.[26]

Length of Hospital Stay

Seven studies reported on this outcome.[12,22-27] Patients in the UAE group had significantly shorter hospital stay compared with the myomectomy group; a

statistically significant (< 0.05) *P* value was reported in five of these studies.[22-25,27]

UAE Versus UAO

Change in Symptoms

Five studies reported on this outcome.[29-33] Reduction in abnormal uterine bleeding or reduction in pelvic pressure was observed between three months and one year after the procedure in both groups. There were no statistically significant differences found between UAE and UAO.

Complications

Four studies reported on this outcome.[30-33] Post-procedural pain in the UAE group was significantly more severe than the UAO group in three studies, with the number of patients ranging from 14 to 58. In one non-randomized study, treatment with UAE was related to significantly higher complication rates than treatment with UAO. The complications observed in the UAE group included fever, spasm of the uterine artery, sloughing of myoma, hematoma of the procedure site, deep venous thrombosis, allergic reaction, decreased ovarian reserve, and decreased libido.

Reproductive Outcomes

Two studies reported on this outcome.[33,34] One non-RCT[33] indicated that no statistically significant difference was detected between UAE and UAO with respect to the number of pregnancies or deliveries, mean gestational week of the newborn, and risk of preterm delivery. Results from another non-RCT[34] showed that the UAE group was associated with more abortions ($P < 0.05$) and more Caesarean sections ($P > 0.05$) than the UAO group.

Re-intervention

Two studies reported on this outcome.[32,33] The risk of re-intervention during the first six months after the initial procedure was similar between UAE and UAO in one study,[32] but significantly higher in the UAE group in another[33] (39% in the UAE group versus 15% in the UAO group; $P = 0.001$).

Length of Hospital Stay

Four studies reported on this outcome.[30-33] Most of the studies reported equivalent length of hospital stay between UAO and UAE, except that in one RCT,[32] the average length of hospital stay was 57 hours for patients treated with UAE, compared with 46 hours for patients in the UAO group ($P = 0.001$).

UAE Versus MRgFU (One Study[35])

Change in Symptoms

Patients in the UAE group reported significantly greater improvement in Symptom Severity Score in the UFS-QOL three months after the procedure, compared with those in the MRgFU group ($P < 0.001$).

Health-Related Quality of Life

Patients in the UAE group had a greater improvement in quality of life (measured by the total score of the HRQoL subscales on the UFS-QOL; the HRQoL subscales assess the impact of fibroid-related symptoms on women's quality of life from the aspects of "concern, activities, energy/mood, control, self-consciousness and sexual function"[41]) three months after the procedure, compared with those in the MRgFU group ($P < 0.001$).

Complications

There were no adverse events reported in the MRgFU group, while 13 adverse events were reported among the 68 patients in the UAE group: two patients had endometritis, two had premature ovarian failure and related amenorrhea, one developed an infected hematoma at the procedure site, one had a vulvar abscess due to non-target embolization, and seven patients experienced painful spontaneous expulsion of the treated uterine fibroid six to 12 weeks after UAE.

Re-interventions

The risk of requiring re-intervention one year after the primary procedure was higher in patients treated with MRgFU, compared with those treated with UAE (35% vs. 4.5%, $P = 0.002$). Reasons for the re-interventions were not specified.

MRgFU Versus Hysterectomy (One Study[36,42])

Change in Symptoms

In the MRgFU group, patients' Symptom Severity Score in the UFS-QOL reduced from 61.7 at baseline to 37.7 six months after the procedure ($P < 0.0001$). For the Symptom Severity scale, a 10-point reduction was considered a clinically meaningful symptom improvement.

Health-Related Quality of Life

At six-month follow-up, improvements from baseline in all subscales in the SF-36 were reported in both treatment groups. Statistically significant between-group differences were observed in the subscales of Bodily Pain, General Health, Vitality, and Mental Health, favouring hysterectomy.

Complications

Compared with hysterectomy, fewer patients in the MRgFU group reported procedure-related complications, such as fever and transfusion. Four patients in the hysterectomy group required unintended interventions (removal of foreign body from the bladder or surgical repair of hernia or iatrogenic colonic lesion) for treatment-related complications, while none of the MRgFU patients group did. Fewer patients in the MRgFU group experienced adverse events than those in the hysterectomy, 81% versus 99%, respectively, $P < 0.0001$. The most common adverse events were pain and/or discomfort, gastrointestinal tract events, dermatological conditions, and nervous system events. At six-month follow-up, there was no statistically significant difference in the risk of serious adverse events between groups (8% in the MRgFU group and 10% in the hysterectomy group). One case of SAE was reversible sciatic nerve palsy following the treatment of MRgFU. Other SAEs were not specified.

Re-interventions

Prior to the six-month follow-up, four patients (3.7%) in the MRgFU group required re-interventions for continued or recurrent fibroid-related symptoms, three hysterectomies, and one UAE.

Laparoscopic Myomectomy Versus Laparoscopic RFVTA (One Study[37])

Change in Symptoms

Patients in the myomectomy group reported a greater reduction in bleeding compared with RFVTA one year after the treatment, but the between-group difference was not statistically significant. In addition, there was no statistically significant difference in improvement in pelvic pressure between the two groups.

Health-Related Quality of Life

There was no statistically significant difference in EQ-5D score between the two treatment groups.

Complications

Patients in the myomectomy group had greater blood loss during the procedure compared with those in the RFVTA group (51 mL versus 16 mL, $P < 0.001$). It was unclear whether the between-group difference was clinically important, given the small volume of blood.

Re-intervention

Patients in the myomectomy group did not require further interventions, while three additional interventions were required in the RFVTA group: two hysterectomies (one patient had hypermenorrhea shortly after the ablation, and hysterectomy was eventually performed to treat the uterine perforation that resulted from dilation and curettage for hypermenorrhea; the second hysterectomy was performed due to a suspension of smooth muscle tumour of uncertain malignant potential from biopsy) and one myomectomy as per patient's preference (asymptomatic but had a desire for pregnancy).

Patient Satisfaction

At 12-month follow-up, more patients in the myomectomy group reported being "very satisfied" with the treatment effect on the symptoms than those in the RFVTA group (86.5% versus 42.9%, $P = 0.004$).

Length of Hospital Stay

The length of hospital stay was significantly longer in the myomectomy group than in the RFVTA group (29.9 hours versus 10.0 hours, respectively; $P < 0.001$).

Economic Review

Study Characteristics

Data from seven unique economic evaluations, published between 2004 and 2015, were identified for inclusion and presented in eight publications.[4,43-49] Details of the economic evaluations are presented in the tables in Appendix 8.

All economic evaluations were cost-utility analyses based on decision analytic models. Utilities were derived from the clinical literature, based on expert opinion, or collected from patients enrolled in a corresponding clinical trial. Four evaluations were performed in the United States with an American societal perspective,[4,44,45,49] two in the United Kingdom from a public-payer perspective,[46-48] and one evaluation was performed in Canada with an Ontario public-payer perspective.[43] The studies examined the cost-effectiveness of UAE,[4,43-49] MRgFU,[4,43-45,47] myomectomy,[4,43,44,47] hysterectomy,[4,43,45-49] and pain management with pharmacotherapy[4] for the treatment of symptomatic uterine fibroids in premenopausal women. In particular, one of the UK evaluations compared MRgFU against current practice, defined based on the assumption that patients would be distributed to various first-line treatments: 25% receiving UAE, 25% receiving myomectomy, and 50% receiving hysterectomy.[47] Five of the seven economic models had an 11-year time horizon ending at the assumed age of menopause (51 or 55),[43,45,46,48,49] although one study included a time horizon of five years (chosen due to limited data reported beyond five years),[44] and the final study included a lifetime horizon.[4] Four studies reported receiving funding from industry or had authors who disclosed financial ties with industry.[4,44,45,47]

Model inputs included patient eligibility for each treatment modality, probabilities of symptom relief and recurrence, probability of complications, and intervention-related costs. Of the majority of economic evaluations that included patient eligibility for each procedure in the model, eligibility was set at 100% for hysterectomy and myomectomy, 90% for UAE, and 35% for MRgFU because a proportion of patients may not be eligible due to the size and/or location of the fibroids.[4,43-45] If a patient was considered ineligible for a particular procedure, she was generally, but not always, assumed to receive the least invasive of the remaining treatment options, with the level of invasiveness typically increasing from MRgFU to UAE to myomectomy to hysterectomy.[43-45] These probability estimates were mainly taken from reports in the clinical literature. Cost inputs for the economic models included physician and other staff costs,[4,43,45-49] direct medical costs including hospital services,[4,43-49] laboratory and/or screening costs,[4,43-45] productivity costs,[4,44-46,48,49] and costs related to equipment maintenance and operation.[4,43,47] All economic models, except for the Canadian analysis by Babashov et al.,[43] included costs associated with procedure-related complications. The cost inputs for the Canadian economic evaluation included pre-, peri-, and post-procedural resource use.[43] The pre-procedural costs for women with symptomatic uterine fibroids included one consultation with a gynecologist, one consultation with a radiologist or surgeon, one ultrasound, and lab tests (a complete blood count and creatinine test). If patients proceeded to surgery, they would also have one consultation with an anesthesiologist. Patients pursuing UAE or MRgFU would receive a diagnostic MRI to determine procedural eligibility. Professional fees associated with the pre-procedural ultrasound and MRI were also included. Peri-procedural costs included staff costs and professional fees, and direct procedural and supply costs. Within the first six months after treatment, all patients were assumed to receive one ultrasound and have one follow-up appointment with a radiologist or gynecologist. It was assumed that patients would not experience significantly costly complications after discharge; disutilities rather than costs were applied to post-procedure complications. The Canadian evaluation also included a budget impact analysis examining the one-year cost burden of implementing MRgFU to replace other uterine fibroid treatments from the perspective of the Ontario Ministry of Health and Long-Term Care.[43]

In general, patients with symptom recurrence would be re-treated with the same intervention,[4,43,45] while patients who experienced treatment failure would proceed to a treatment with a more invasive modality.[4,43-45,47,49] The number of rounds of re-treatment specified in the models were variable, although in all cases, hysterectomy was the third-line treatment for symptom recurrence. Complete symptom resolution was assumed after hysterectomy,[45,46,48,49] and symptom recurrence was assumed not to occur after menopause.[4,43]

Critical Appraisal of Individual Studies

In general, the authors of the economic evaluations used valid and well-reported methods to conduct their analyses. All studies clearly specified their research questions, choice of economic evaluation and perspective, interventions, and comparators, as well as primary outcomes.[4,43-47,49] All evaluations stated their sources for model parameter estimates; however, several did not provide details of the study characteristics or discuss the potential quality (e.g., risk of bias) in the results (when the estimates were derived from a single study)[4,44,45,49,50] or the methods of meta-analysis when synthesizing multiple studies to produce a single model parameter estimate.[4,45,48,50] All studies used quality-adjusted life-years (QALYs) to quantify clinical benefits, but the details of the patients from whom

utilities were collected were not always clearly described.[4,45,47,49] In cases where published data were unavailable, inputs were based on expert opinion, which may not truly reflect the patient experience. Six studies captured the costs associated with lost productivity,[4,44-46,48,49] although four studies[4,44,45,49] had chosen the broader societal perspective in which these costs would be relevant, and two[46,48] included these costs, which was inconsistent with the stated perspective. In one of these studies, the analysis was separately presented for the health care payer and societal perspective.[49] Methods for the estimation of costs were generally well described, but only one evaluation clearly reported the quantities of resource use separately from the unit costs.[43] In particular, the Canadian study[43] did not capture the costs of treating complications, which may have caused the expected cost of the treatments strategies to be underestimated, especially given that the rate of complications differs between the various interventions.

All studies provided details on the model structure, and overall, the assumptions and key parameters supporting these models were well described. Sources for model parameters varied between studies, with some citing a single source, while others pooled data from multiple studies, and it was unclear whether the methods used to combine multiple data sources were appropriate.[44] Two studies did not include myomectomy as a first-line treatment option for uterine fibroids, although the authors acknowledged that myomectomy was a surgical alternative to hysterectomy, and it was a treatment option for UAE failure in the model.[45,46,48] All economic evaluations stated the time horizons and discount rates applied in the analyses. The time horizon was limited to five years in one study.[44] All other evaluations had a time horizon of at least 11 years, and given that premenopausal patients, especially younger patients, may experience symptom recurrence beyond five years from initial treatment when undergoing less-invasive treatment modalities, this model may have missed relevant long-term health care costs. The authors discussed this limitation of their model, but justified their choice by commenting that at the time of publication, there were no clinical data beyond five years of follow-up. Other studies assumed a constant risk of recurrence (derived from literature reviews or expert opinion) in each cycle of the model until the patient reached menopause, and tested a range of recurrence rates in sensitivity analyses.[4,43,45,49]

Most studies used appropriate approaches to evaluate the uncertainty surrounding model parameters and structure (such as practice patterns, age, recurrence rate, complication rate, health-related quality of life, transition probabilities, and treatment costs) in the sensitivity analyses, with one publication explicitly reporting the distribution for the model parameters.[44] However, sensitivity analyses were not performed for a number of relevant variables, such as costs other than those associated with loss of productivity, in two publications based on the HOPEFUL study.[46,48] Overall, results and conclusions of the economic analyses were presented clearly and with relevant caveats discussed.

Three of the economic evaluations examining focused ultrasound were sponsored by the manufacturers.[4,44,47]

Strengths and limitations of the included economic evaluations are provided in Appendix 9.

Results

The majority of included economic evaluations indicated that MRgFU is the most cost-effective option for the treatment of symptomatic uterine fibroids in the evaluated base case[4,45,47] or in certain scenarios (when hysterectomy or UAE are not available options and when all patients are eligible for MRgFU)[43] or sensitivity analyses (varying the parameters for quality of life, costs of treatments and complications, and probabilities of symptom relief and recurrence).[44] At a willingness-to-pay threshold of $50,000/QALY, two economic evaluations conducted from an American societal perspective showed that MRgFU was more cost-effective than UAE and hysterectomy,[45] or when compared to UAE, hysterectomy, and myomectomy.[4] MRgFU was also the dominant intervention (i.e., less costly but more effective) in the base-case analysis of an economic evaluation from a public-payer perspective when compared with UAE, myomectomy, and hysterectomy.[47] These three evaluations[4,45,47] each assumed no major or minor complications with MRgFU. MRgFU remained the dominant strategy in several scenario analyses that adjusted the distribution of patients to each treatment modality, recurrence rates, utilities, complication rates, and hospital costs. Another economic evaluation indicated that, from an American societal perspective and at a willingness-to-pay of $50,000/QALY, MRgFU was more cost-effective than myomectomy when productivity costs were considered, and more cost-effective than UAE regardless of whether productivity costs were considered.[44]

However, the Canadian economic evaluation[43] demonstrated that MRgFU was only more cost-effective than UAE in a scenario analysis when all patients were assumed to be eligible for MRgFU. For the base case when patient eligibility for MRgFU was set at 35%, UAE was more cost-effective than MRgFU, hysterectomy, and myomectomy at a willingness-to-pay of $46,480/QALY or greater. MRgFU and myomectomy were both dominated (i.e., more costly, less effective) by the other treatment strategies in the base case, and therefore would not be considered cost-effective at any decision threshold. A 35% eligibility rate for MRgFU in the base case was based on estimates derived from the clinical literature and was a value common to all economic models that evaluated this parameter; therefore, this is likely the more realistic scenario than assuming 100% eligibility for MRgFU and suggests that it would not be cost-effective in current clinical practice in Canada. Probabilistic sensitivity analyses incorporating parameter uncertainty demonstrated that UAE was most often the most cost-effective option compared with hysterectomy, MRgFU, and myomectomy at a willingness-to-pay threshold of at least $46,480/QALY; MRgFU was the most cost-effective option in 20% of the cases when willingness-to-pay was $50,000/QALY. One-way sensitivity analyses suggested that the findings on MRgFU are most sensitive to the utility values for symptomatic fibroids and symptom relief, a lower procedural cost for MRgFU, a lower recurrence rate for MRgFU or myomectomy, and when the proportion of patients eligible for MRgFU increased.

Of the economic evaluations that did not include MRgFU in the analysis, UAE dominated hysterectomy (i.e., was less costly and more effective) for the treatment of symptomatic uterine fibroids from an American societal perspective,[49] and was less costly (£2,536 versus £3,282) but less effective (8.203 QALYs versus 8.241 QALYs) than hysterectomy in a UK public-payer perspective.[46,48] The UK study noted that UAE was dominant to hysterectomy in the first year of treatment, but in the subsequent years, UAE incurred additional costs due to symptomatic fibroid recurrence and fewer QALYs than

hysterectomy. Overall, in considering the complete time horizon (i.e., until patients reached menopause), the analyses suggest that UAE was less costly but also provided fewer QALYs under the assumption that the cohort's age was 44 years, and was dominated by hysterectomy if the cohort was younger (age at first procedure is 35).[46]

Details of the findings of economic evaluations are presented in the tables in Appendix 10.

Discussion

Summary of Evidence

Ten RCTs and 16 non-randomized studies in women with symptomatic uterine fibroids met the inclusion criteria of this review. The uterine-preserving interventions examined in these studies were myomectomy, UAE, UAO, MRgFU, and RFVTA. They were either compared with the conventional treatment for symptomatic uterine fibroids (hysterectomy), or were compared with another minimally invasive intervention. UAE was investigated in 21 studies (versus hysterectomy in six studies, versus myomectomy in seven studies, versus UAO in six studies, versus MRgFU in one study, and versus hysterectomy or myomectomy in one study), myomectomy in 12 studies (versus hysterectomy in three studies, versus UAE in seven studies, versus RFVTA in one study, and versus hysterectomy or UAE in one study), UAO in six studies (all versus UAE), MRgFU in two studies (versus UAE or hysterectomy), and RFVTA in one study (versus myomectomy).

In general, small sample sizes in most of the studies limited the quality of the evidence. Interpretation of study results was challenging due to imbalanced patient baseline characteristics between treatment groups, particularly in non-randomized controlled trials, as well as the insufficient power of the study to detect meaningful differences in study outcomes. Meta-analysis of the outcome measures was not performed due to the heterogeneity of data reporting.
In summary:

- UAE improved bulk symptoms such as pelvic pain and pressure and improved patient's quality of life from baseline. It was superior to myomectomy in reducing abnormal uterine bleeding, and had a lower risk of peri-procedural complications such as blood loss, shorter hospital stay, and higher patient satisfaction compared with hysterectomy and myomectomy. However, UAE was associated with a higher risk of re-intervention compared with UAO.
- Myomectomy was associated with improved pelvic pressure symptoms, reduced menorrhagia, and improved quality of life from baseline. It was associated with higher pregnancy rates (data were from a study comparing myomectomy and UAE, although UAE was not recommended for women who desire future pregnancy).
- UAO reduced abnormal uterine bleeding and improved bulk symptoms from baseline. It was associated with a lower risk of complications compared with UAE.
- RFVTA improved abnormal uterine bleeding and improved quality of life from baseline. It was linked to a lower risk of complications, such as blood loss during the procedure (versus myomectomy) and shorter hospital stay (than myomectomy); however, RFVTA was also linked to

more re-interventions in the future (than myomectomy), due to fibroid recurrence or insufficient symptom control.

- MRgFU improved fibroid-related symptoms and quality of life from baseline. It was associated with a lower risk of overall complications but a higher risk of re-intervention compared with UAE and hysterectomy.

Hysterectomy was found to be superior to UAE and other less-invasive interventions (such as myomectomy and MRgFU) in improving patient's quality of life, both generic and disease-specific. This is not surprising, because hysterectomy ultimately eliminates fibroid-related symptoms, especially heavy uterine bleeding, and subsequently enhances patient's well-being. However, minimally invasive interventions such as UAE, RFVTA, and MRgFU were associated with fewer peri-operative and post-operative complications, shorter hospital stay, and more patient satisfaction compared with hysterectomy in short-term follow-up. On the other hand, in the long term they are related to more fibroid recurrence and more re-interventions, which may eventually negatively impact economics and patient satisfaction. The included clinical studies generally had short study durations; therefore, we were not able to examine the long-term effect of an intervention on patient satisfaction.

Although the SOGC practice guidelines suggest UAE as an alternative to surgery in women who wish to preserve their uterus and who are not concerned about future fertility,[3,51] data on reproductive outcomes were available in a few included studies and suggested that women treated with UAE had less favourable outcomes than myomectomy, for rates of becoming pregnant and complications of delivery. It is unclear why these women were enrolled in these studies when UAE is not recommended for women who wish to become pregnant. These studies added supportive evidence to the SOGC recommendations, which advise that reproductive capacity and pregnancy may be negatively affected. Because the data were derived from a subgroup of patients in the original studies, they should be considered with caution.

Several systematic reviews and meta-analyses have been published in recent years.[1,52-54] Their results are generally consistent with the current review: UAE, UAO, and MRgFU were found to have higher re-intervention rates than hysterectomy and myomectomy; UAE patients had less blood loss during the procedure than patients who underwent surgery, and had a shorter hospital stay. In a systematic review conducted by Panagiotopoulou et al. published in 2013, two RCTs comparing UAE and myomectomy and three RCTs comparing UAE and UAO were included.[53] Results from indirect analysis showed that myomectomy and UAE were related to higher patient satisfaction than UAO. UAE and UAO were also associated with higher re-intervention rate compared with myomectomy. Comparable complication rates were observed among these three interventions. All five trials have been included in the current review. In a Cochrane review published in 2014,[1] seven RCTs (UAE was compared with abdominal hysterectomy in three, UAE was compared with myomectomy in two, and UAE was compared with hysterectomy or myomectomy in two) with 793 patients were included. Results of this review suggested that there were no statistically significant differences in patient satisfaction between UAE and surgical intervention within two years following the procedure. The differences at five-year follow-up were not statistically significant, either. In addition, UAE was associated with more future interventions compared with myomectomy and hysterectomy. Data from a selected subgroup in a small study suggested that

myomectomy could be related to better fertility outcomes than UAE. One of the included studies in the Cochrane review was excluded in our review because patients underwent myomectomy combined with hysterectomy in this study, and there were no separate results reported for each surgery. The systematic review conducted by van der Kooij et al. evaluated the treatment effect of UAE versus surgery (myomectomy or hysterectomy) on symptomatic fibroids.[54] Data from four RCTs enrolling 515 patients suggested that UAE was related to less blood loss and shorter hospital stay in the short term. The longer-term data (up to five years after the procedure) indicated comparable health-related quality of life between interventions of interest, but higher re-intervention rates were reported in the UAE patients. Three RCTs in this review are also included in our review, but the Randomized trial of Embolization versus Surgical Treatment for fibroids (REST) study in the van der Kooij review was excluded because myomectomy and hysterectomy were mixed in one of the treatment arms. One systematic review conducted by Pron et al. investigated the effectiveness of MRgFU with other minimally invasive uterine-preserving interventions and surgeries in patients with uterine fibroids.[52] Two systematic reviews, two RCTs (examining ultrasound-guided focused ultrasound, but not MRgFU), 45 cohort study reports, and 19 case reports were included. Findings from this review suggested that MRgFU reduced fibroid-related symptoms but had high re-treatment rate when the fibroids couldn't be destroyed completely. There was no RCT evidence for MRgFU identified in the Pron review. Although there is a lack of comparative data, the authors suggested MRgFU may be a non-invasive alternative to hysterectomy for women who fail medical therapy.

The investigated uterine-preserving interventions are not always available for women with symptomatic uterine fibroids. For instance, in Ontario, two medical centres have the appropriately trained staff and necessary equipment to perform MRgFU.[43] UAO is not routinely practised in Canada, as the skill set required (if performed laparoscopically) is not widely available, and the equipment is not commercially available (if vaginal occlusion is considered). In the included UAO studies conducted in the United States or the countries in Europe, Africa, and Asia, the uterine arteries were occluded laparoscopically, with the use of vascular clips, coagulation forceps, or microcoils. In addition, the experience of the clinician plays a role in the rates of procedure failure, procedure-related complications, and symptom relief.[55]

Tissue morcellation is a technology that divides uterine tissue into smaller pieces so that it can be removed through a small incision in the abdomen. It is widely used in gynecologic surgery to facilitate the removal of large uteri or myomas while avoiding a traditional laparotomy.[56] Both Health Canada and the US Food and Drug Administration have raised safety concerns regarding the use of power morcellation during myomectomy or hysterectomy, mainly due to the potential seeding or spreading of undiscovered malignancy in the uterus.[57,58] Research looking at the benefits and risks of power morcellation has shown that it does increase the risk of major and minor intraoperative complications, although increased surgeon experience may help to mitigate this risk.[59] The risk of leiomyosarcoma morcellation was balanced by procedure-related complications that were associated with laparotomy.[60] In our review, none of the studies with a treatment arm of myomectomy or hysterectomy specified whether morcellation was employed and what type of morcellation was used during the procedure. None of these studies reported the occurrence of malignancies. Guidance from the SOGC recommends that techniques that minimize specimen disruption and intra-abdominal spread should be considered; assessment for potential

malignancy should be performed in women presenting with uterine fibroids; uterine morcellation should not be used in women with established or suspected cancer, and a total abdominal hysterectomy should be performed instead in these cases; and appropriate training and experience are required in morcellation techniques.[56]

Eight economic evaluations from Europe and North America provided evidence on cost-effectiveness of uterine-preserving interventions in women with symptomatic uterine fibroids. The inputs used in the economic models regarding probabilities of symptom relief and major complications were variable, consistent with the clinical findings of this review; discrepancies may account for different conclusions between the economic and clinical results. For example, two economic analyses[43,44] differed from the clinical findings of this report by assuming a higher probability of symptom relief and risk of major complications with UAE than with myomectomy. However, other economic models used inputs that agree with the clinical results of the comparison between UAE and myomectomy, assuming equal probabilities of symptom relief with both treatment options[4,45] and greater risk of complications following myomectomy than UAE.[4,45,47] In addition, different interventions were predominantly assessed by the clinical versus economic studies identified in this report; five economic models[4,43-45,47] examined the cost-effectiveness of MRgFU compared with several other treatment options, while two studies[35,36] evaluated the clinical effectiveness of MRgFU compared with UAE or hysterectomy. Contrary to the clinical studies, the five economic models input a higher probability of symptom relief with MRgFU than UAE, yet they agreed with the clinical studies by assuming a lower rate of complications following MRgFU than UAE or surgery. None of the economic analyses evaluated the cost-effectiveness of RFVTA or UAO. The cost-effectiveness of less-invasive interventions was influenced by a number of factors, including patient age or the proportion of patients eligible to receive MRgFU, which should be considered when applying the findings from economic models to particular clinical contexts.

Limitations

Inconsistent and conflicting results on the effectiveness and safety of uterine-preserving interventions were commonly reported in the included clinical studies. This is partly explained by the small sample sizes and incomparable patient baseline characteristics. For instance, compared with patients in the myomectomy group, those in the UAE group were older, had had more previous pregnancies, and had poorer baseline quality of life, with larger fibroid size and more severe symptoms.

In the included studies, clinical outcomes were measured and reported in different manners, and various instruments were adopted in measuring the changes in symptoms before and after treatment. Quantitative synthesis was not performed in this review, due to the significant heterogeneity across the studies.

Surgical interventions for symptomatic uterine fibroids can be performed using a variety of methods. For instance, the type of hysterectomy and route of access were not standardized and were often left to the discretion of the attending gynecologist in the identified studies. Likewise, myomectomy was carried out via the abdominal route using laparoscopy or open (laparotomy) incision, or via the vaginal route using hysteroscopy. The route of procedure considerably influences some of the clinical outcomes. For instance, laparoscopic or vaginal surgery are associated with less post-operative pain, fewer peri-operative complications, and

quicker recovery compared with abdominal hysterectomy.[61] In the included studies for this review, study results were reported for patients receiving any type of surgical interventions, and there were no separate results for the aforementioned subgroups of patients (laparoscopy versus laparotomy, hysteroscopy versus laparotomy), or the method of an intervention was not specified. Therefore, we are not able to examine the clinical benefits and risks from a specific method of performing an investigated intervention.

Another challenge is the difficulty in comparing approaches that are fibroid location–specific. For example, a submucosal uterine fibroid may be better managed by hysteroscopic myomectomy,[2,3] which is a day procedure with minimal recovery or pain, versus a large serosal fibroid managed by abdominal or laparoscopic myomectomy.[2] Although both are examples of myomectomy, the outcomes can vary significantly.[6] The comparators also vary because a simple intrauterine fibroid (e.g., 2 cm in diameter) will not likely be managed with UAE, so no comparison is possible here.

The development of imaging techniques, such as the ultrasound-guided radiofrequency ablation therapy, allows for more precise targeting and less-invasive surgical treatment options for uterine fibroids.[62] The effectiveness of imaging-guided thermal therapy in reducing symptoms has been demonstrated in women with symptomatic uterine fibroids, but there is a lack of evidence of the benefits and harms of this type of technology relative to other less-invasive interventions.[63]

Limited evidence was available for long-term clinical effectiveness and safety for the uterine-preserving interventions for women with symptomatic uterine fibroids. In addition, evidence on the benefits and risks of endometrial ablation were not identified through the literature search.

The economic evaluations were limited in the generalizability of their results to current Canadian clinical practice. Of the seven unique economic evaluations identified for this report, one was conducted by a Canadian group with an Ontario public-payer perspective. The applicability of the economic evaluations was further limited by the choice of interventions assessed. Five of the seven evaluations focused on the comparative cost-effectiveness of MRgFU; however, MRgFU is not widely practised in Ontario, and it is unclear whether this procedure is performed elsewhere in Canada. A scenario analysis eliminating MRgFU as a treatment option was not performed. Two economic evaluations did not include MRgFU in their analyses and compared UAE with hysterectomy. These were conducted by groups in the United Kingdom[46] and United States;[49] therefore, it is unclear whether their cost-effectiveness results would be relevant to a Canadian context, given that costing and resource utilization is less transferable across jurisdictions. Guidance on the suitable candidates for the treatment of MRgFU was inconsistent in previous research. Treatment of one single fibroid at a time was recommended in the SOGC guidelines,[3] while no more than five fibroids were suggested in another study.[64] In one of the included studies that compared MRgFU with UAE, 76% of the MRgFU patients had multiple fibroids and 20% of them had more than six fibroids.[35] The number of fibroids was not reported in another study that compared MRgFU with hysterectomy.[36]

Another limitation of the economic evaluations was the limited amount of clinical literature regarding MRgFU supporting the model assumptions. For the Canadian study in particular, several model parameters regarding treatment eligibility and effectiveness were based on results reported in a single publication by O'Sullivan

et al.[4] However, the authors attempted to address uncertainty regarding treatment eligibility, probabilities of symptom relief and recurrence, probabilities of complications, and utilities by conducting sensitivity analyses. Re-intervention is an important outcome in fibroid studies. Repeat procedures or more aggressive therapy such as hysterectomy would potentially be performed after the initial intervention due to insufficient symptom control or fibroid recurrence.

Conclusions and Implications For Decision- Or Policy-Making

Evidence from 26 studies on the clinical effectiveness and safety of procedures to manage symptomatic uterine fibroids, with a focus on uterine-preserving interventions, was reviewed. Study findings suggested that:

- UAE, myomectomy, UAO, RFVTA and MRgFU reduced fibroid-related symptoms and enhanced patient quality of life from baseline.
- UAE was superior to myomectomy in reducing abnormal uterine bleeding. Compared with myomectomy and hysterectomy, UAE had a lower risk of peri-procedural complications, shorter hospital stay, and higher patient satisfaction. However, it was associated with a higher risk of re-intervention compared with UAO.
- Myomectomy was superior to UAE in improving bulk symptoms. It was also reported to have better pregnancy outcomes than UAE, based on limited clinical evidence.
- UAO was associated with a lower risk of complications compared with UAE.
- RFVTA had a lower risk of peri-procedural complications, had shorter hospital stay, and was linked to more re-interventions in the future, compared with myomectomy.
- MRgFU was linked to fewer complications but more re-interventions, compared with UAE and hysterectomy.

The quality of these studies was low due to small sample sizes and study design. Inconsistent results were observed across the included studies. In addition, the amount of available evidence is limited and some of the recruited patients in the included studies may not be suitable candidates for a particular treatment, which limits the applicability of the evidence across treatments. Therefore, results should be interpreted with caution, especially for the outcomes that were examined only in a subgroup of study participants; for example, the reproductive outcomes that were evaluated in patients who wished to conceive following UAE.

Findings from a Canadian economic evaluation demonstrated that UAE was more cost-effective than hysterectomy for the treatment of symptomatic uterine fibroids at a willingness-to-pay threshold of $46,480 or greater, and that UAE was the dominant intervention (i.e., more effective and less expensive) when compared with myomectomy and MRgFU.

Uterine size, symptom severity, patient preference, desire for pregnancy, and available facilities may influence the selection of appropriate uterine-preserving interventions for symptomatic uterine fibroids.

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62. Shen SH, Fennessy F, McDannold N, Jolesz F, Tempany C. Image-guided thermal therapy of uterine fibroids. Semin Ultrasound CT MR [Internet]. 2009 Apr [cited 2015 Sep 25];30(2):91-104. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2768544

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64. Roberts A. Magnetic resonance-guided focused ultrasound for uterine fibroids. Semin Intervent Radiol [Internet]. 2008 Dec [cited 2015 Sep 28];25(4):394-405. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3036536

65. Hehenkamp WJ, Volkers NA, Birnie E, Reekers JA, Ankum WM. Pain and return to daily activities after uterine artery embolization and hysterectomy in the treatment of symptomatic uterine fibroids: results from the randomized EMMY trial. Cardiovasc Intervent Radiol. 2006 Mar;29(2):179-87.

66. Hehenkamp WJ, Volkers NA, Bartholomeus W, de Blok S, Birnie E, Reekers JA, et al. Sexuality and body image after uterine artery embolization and hysterectomy in the treatment of uterine fibroids: a randomized comparison. Cardiovasc Intervent Radiol [Internet]. 2007 Sep [cited 2015 May 28];30(5):866-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2039794

67. Mara M, Fucikova Z, Maskova J, Kuzel D, Haakova L. Uterine fibroid embolization versus myomectomy in women wishing to preserve fertility: preliminary results of a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2006 Jun 1;126(2):226-33.

68. Hald K, Noreng HJ, Istre O, Klow NE. Uterine artery embolization versus laparoscopic occlusion of uterine arteries for leiomyomas: long-term results of a randomized comparative trial. J Vasc Interv Radiol. 2009 Oct;20(10):1303-10.

69. Moss JG, Cooper KG, Khaund A, Murray LS, Murray GD, Wu O, et al. Randomised comparison of uterine artery embolisation (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): 5-year results. BJOG. 2011 Jul;118(8):936-44.

70. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ [Internet]. 1996 Aug 3 [cited 2015 Aug 6];313(7052):275-83. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2351717

Appendix 1: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 7, 2015
Alerts:	Bi-weekly search updates began May 21, 2015 and ran until November 24, 2015.
Study Types:	Health technology assessments; systematic reviews; meta-analyses; randomized controlled trials; controlled clinical trials; cohort studies; economic studies; and guidelines
Limits:	Publication date limits: • Randomized controlled trials, controlled clinical trials, cohort studies and economic studies — no date limits • Health technology assessments, systematic reviews, meta-analyses, and guidelines — 2005–present Language limit: English or French Conference abstracts: excluded Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab .kw	Abstract Author keyword
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn .yr	CAS registry number Publication year
.la	Language
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	exp leiomyoma/
2	exp myoma/ and (uterus/ or myometrium/)
3	(fibroma* and (uter* or myometr*)).ti,ab,kw,hw.

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
4	(fibroid* or fibromyoma* or fibroleiomyoma* or leiomyoma* or angiomyoma* or leiomyomatosis or angioleiomyoma* or elastomyofibroma* or hemangioleiomyoma* or hemangiomyoma* or leimyoma* or leiomyoma* or leyomyoma* or myofibroma* or myoma* or (smooth muscle adj2 tumo?r*)).ti,ab,kw.
5	or/1-4
6	uterine artery embolization/ or embolization, therapeutic/
7	(emboliz* or embolis* or embolotherapy or UAE).ti,ab,kw.
8	endometrial ablation techniques/
9	((endometrial or endometrium) adj3 (ablat* or resect*)).ti,ab,kw.
10	(myolysis or cryomyolysis).ti,ab,kw.
11	(MRgFU or MRIgFUS or iMRI or MR-HIFU or MRHIFU).ti,ab,kw.
12	((MR or MRI or magnetic resonance) adj4 (ultrasound or ultrason* or ultra-sound or ultra-son* or sonograph* or "U/S")).ti,ab,kw.
13	(HIFU or USgHIFU or (high intensity adj3 (ultrasound or ultrason* or ultra-sound or ultra-son*))).ti,ab,kw.
14	High-Intensity Focused Ultrasound Ablation/
15	(PMWA or RFVTA or USgRFA or TBA or ablat*).ti,ab,kw.
16	Magnetic Resonance Imaging, Interventional/
17	exp Ultrasonic Therapy/
18	((ultrasound or ultrason* or ultra-sound or ultra-son* or sonograph*) adj2 therap*).ti,ab,kw.
19	exp Ultrasonography, Interventional/
20	(interventional adj2 (ultrasound or ultrason* or ultra-sound or ultra-son* or sonograph*)).ti,ab,kw.
21	or/6-20
22	5 and 21
23	uterine myomectomy/
24	(myomatectom* or myomotom* or myomectom* or fibroidectom*).ti,ab,kw.
25	or/23-24
26	22 or 25
27	26 use pmez
28	exp leiomyoma/
29	exp myoma/ and (uterus/ or myometrium/)
30	uterus myoma/
31	(fibroma* and (uter* or myometr*)).ti,ab,kw,hw.
32	(fibroid* or fibromyoma* or fibroleiomyoma* or leiomyoma* or angiomyoma* or leiomyomatosis or angioleiomyoma* or elastomyofibroma* or hemangioleiomyoma* or hemangiomyoma* or leimyoma* or leiomyoma* or leyomyoma* or myofibroma* or myoma* or (smooth muscle adj2 tumo?r*)).ti,ab,kw.
33	or/28-32
34	uterine artery embolization/
35	(emboliz* or embolis* or embolotherapy or UAE).ti,ab,kw.
36	endometrium ablation/
37	((endometrial or endometrium) adj3 (ablat* or resect*)).ti,ab,kw.

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
38	(myolysis or cryomyolysis).ti,ab,kw.
39	high intensity focused ultrasound/ or high intensity focused ultrasound device/ or ultrasound therapy/ or ultrasound surgery/
40	interventional magnetic resonance imaging/
41	radiofrequency ablation/
42	(MRgFU or MRIgFUS or iMRI or MR-HIFU or MRHIFU).ti,ab,kw.
43	((MR or MRI or magnetic resonance) adj4 (ultrasound or ultrason* or ultra-sound or ultra-son* or sonograph* or "U/S")).ti,ab,kw.
44	(HIFU or USgHIFU or (high intensity adj3 (ultrasound or ultrason* or ultra-sound or ultra-son*))).ti,ab,kw.
45	(PMWA or RFVTA or USgRFA or TBA or ablat*).ti,ab,kw.
46	((ultrasound or ultrason* or ultra-sound or ultra-son* or sonograph*) adj2 therap*).ti,ab,kw.
47	(interventional adj2 (ultrasound or ultrason* or ultra-sound or ultra-son* or sonograph*)).ti,ab,kw.
48	or/34-47
49	33 and 48
50	myomectomy/
51	(myomatectom* or myomotom* or myomectom* or fibroidectom*).ti,ab,kw.
52	or/50-51
53	49 or 52
54	53 not conference abstract.pt.
55	54 use oemezd
56	27 or 55
57	limit 56 to english language
58	56 and french.la.
59	or/57-58
60	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
61	Randomized Controlled Trial/
62	Randomized Controlled Trials as Topic/
63	"Randomized Controlled Trial (topic)"/
64	Controlled Clinical Trial/
65	Controlled Clinical Trials as Topic/
66	"Controlled Clinical Trial (topic)"/
67	Randomization/
68	Random Allocation/
69	Double-Blind Method/
70	Double Blind Procedure/
71	Double-Blind Studies/
72	Single-Blind Method/
73	Single Blind Procedure/
74	Single-Blind Studies/

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
75	Placebos/
76	Placebo/
77	Control Groups/
78	Control Group/
79	(random* or sham or placebo*).ti,ab,hw.
80	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
81	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
82	(control* adj3 (study or studies or trial*)).ti,ab.
83	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
84	allocated.ti,ab,hw.
85	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
86	cohort.ti,ab,hw.
87	or/60-86
88	59 and 87
89	exp animals/
90	exp animal experimentation/ or exp animal experiment/
91	exp models animal/
92	nonhuman/
93	exp vertebrate/ or exp vertebrates/
94	or/89-93
95	exp humans/
96	exp human experimentation/ or exp human experiment/
97	or/95-96
98	94 not 97
99	88 not 98
100	meta-analysis.pt.
101	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
102	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
103	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
104	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
105	(data synthes* or data extraction* or data abstraction*).ti,ab.
106	(handsearch* or hand search*).ti,ab.
107	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
108	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
109	(meta regression* or metaregression*).ti,ab.
110	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
111	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
112	(cochrane or (health adj2 technology assessment) or evidence report).jw.
113	(comparative adj3 (efficacy or effectiveness)).ti,ab.
114	(outcomes research or relative effectiveness).ti,ab.
115	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
116	or/100-115
117	59 and 116
118	limit 117 to yr="2005 -Current"
119	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
120	(guideline* or standards or consensus* or recommendat*).ti.
121	(practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti.
122	(care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard)).ti.
123	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti.
124	(algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti.
125	(algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti.
126	or/119-125
127	59 and 126
128	limit 127 to yr="2005 -Current"
129	99 or 118 or 128
130	remove duplicates from 129

OTHER DATABASES	
PubMed	Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used. PubMed is searched for citations not found in MEDLINE.
Cochrane Library	Same MeSH, keywords and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Cochrane Library databases.
Trial registries (Clinicaltrials.gov)	Same keywords and limits used as per MEDLINE search. Search limited to completed trials.

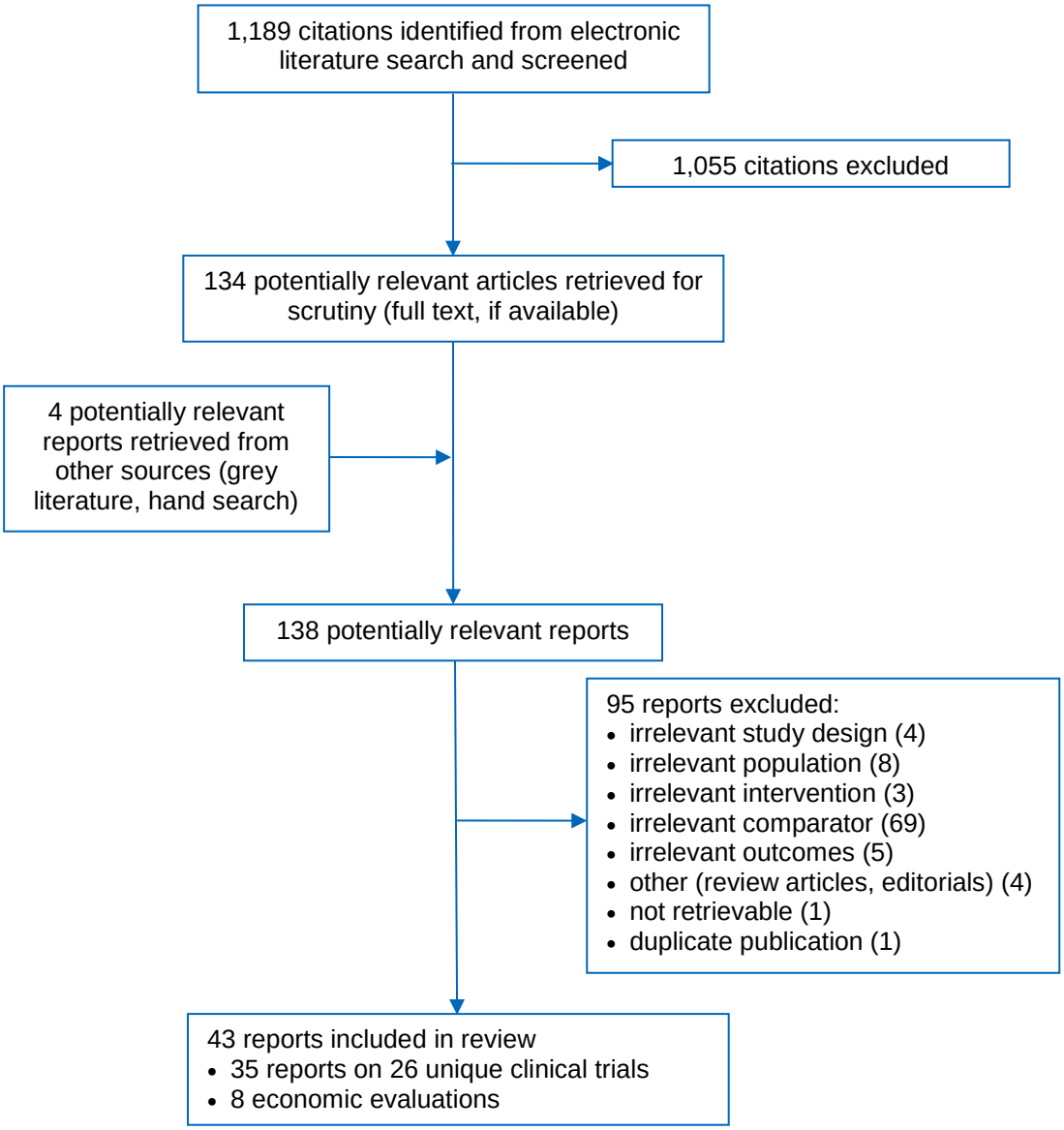
Grey Literature

Dates for Search:	May 2015
Keywords:	Uterine fibroids, fibroids, leiomyoma
Limits:	No publication date limit; English or French language only

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based searching” (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine), were searched:

- Health Technology Assessment Agencies
- Drug & Device Regulatory Approvals
- Advisories & Warnings
- Clinical Practice Guidelines
- Health Economics
- Databases (free)
- Statistics/Prevalences
- Internet Search
- Open Access Journals.

Appendix 2: Selection of Included Studies



Appendix 3: Included Studies For Clinical Evidence

Ambat S, Mittal S, Srivastava DN, Misra R, Dadhwal V, Ghosh B. Uterine artery embolization versus laparoscopic occlusion of uterine vessels for management of symptomatic uterine fibroids. Int J Gynaecol Obstet. 2009 May;105(2):162-5.

Brochner AC, Mygil B, Elle B, Toft P. Inflammatory response in patients undergoing uterine artery embolization as compared to patients undergoing conventional hysterectomy. Acta Radiol. 2009 Dec;50(10):1193-7.

Broder MS, Goodwin S, Chen G, Tang LJ, Costantino MM, Nguyen MH, et al. Comparison of long-term outcomes of myomectomy and uterine artery embolization. Obstet Gynecol. 2002 Nov;100(5 Pt 1):864-8.

Cunningham E, Barreda L, Ngo M, Terasaki K, Munro MG. Uterine artery embolization versus occlusion for uterine leiomyomas: a pilot randomized clinical trial. J Minim Invasive Gynecol. 2008 May;15(3):301-7.

The EMMY study:

Hehenkamp WJ, Volkers NA, Birnie E, Reekers JA, Ankum WM. Symptomatic uterine fibroids: treatment with uterine artery embolization or hysterectomy--results from the randomized clinical Embolisation versus Hysterectomy (EMMY) Trial. Radiology [Internet]. 2008 Mar [cited 2015 May 28];246(3):823-32. Available from: http://pubs.rsna.org/doi/pdf/10.1148/radiol.2463070260

Hehenkamp WJ, Volkers NA, Donderwinkel PF, de Blok S, Birnie E, Ankum WM, et al. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids (EMMY trial): peri- and postprocedural results from a randomized controlled trial. Am J Obstet Gynecol. 2005 Nov;193(5):1618-29.

Volkers NA, Hehenkamp WJ, Birnie E, Ankum WM, Reekers JA. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: 2 years' outcome from the randomized EMMY trial. Am J Obstet Gynecol. 2007 Jun;196(6):519-21.

Hehenkamp WJ, Volkers NA, Birnie E, Reekers JA, Ankum WM. Pain and return to daily activities after uterine artery embolization and hysterectomy in the treatment of symptomatic uterine fibroids: results from the randomized EMMY trial. Cardiovasc Intervent Radiol. 2006 Mar;29(2):179-87.

Hehenkamp WJ, Volkers NA, Bartholomeus W, de Blok S, Birnie E, Reekers JA, et al. Sexuality and body image after uterine artery embolization and hysterectomy in the treatment of uterine fibroids: a randomized comparison. Cardiovasc Intervent Radiol [Internet]. 2007 Sep [cited 2015 May 28];30(5):866-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2039794

van der Kooij SM, Hehenkamp WJ, Volkers NA, Birnie E, Ankum WM, Reekers JA. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 5-year outcome from the randomized EMMY trial. Am J Obstet Gynecol. 2010 Aug;203(2):105-13.

Goodwin SC, Bradley LD, Lipman JC, Stewart EA, Nosher JL, Sterling KM, et al. Uterine artery embolization versus myomectomy: a multicenter comparative study. Fertil Steril. 2006 Jan;85(1):14-21.

Hahn et al.

Hahn M, Brucker S, Kraemer D, Wallwiener M, Taran FA, Wallwiener CW, et al. Radiofrequency volumetric thermal ablation of fibroids and laparoscopic myomectomy: long-term follow-up from a randomized trial. Geburtshilfe Frauenheilkd [Internet]. 2015 May [cited 2015 Jul 2];75(5):442-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4461677

Brucker SY, Hahn M, Kraemer D, Taran FA, Isaacson KB, Kramer B. Laparoscopic radiofrequency volumetric thermal ablation of fibroids versus laparoscopic myomectomy. Int J Gynaecol Obstet [Internet]. 2014 Jun [cited 2015 May 28];125(3):261-5. Available from: http://www.sciencedirect.com/science/article/pii/S0020729214001040

Hald et al.

Hald K, Noreng HJ, Istre O, Klow NE. Uterine artery embolization versus laparoscopic occlusion of uterine arteries for leiomyomas: long-term results of a randomized comparative trial. J Vasc Interv Radiol. 2009 Oct;20(10):1303-10.

Hald K, Kløw NE, Qvigstad E, Istre O. Laparoscopic occlusion compared with embolization of uterine vessels: a randomized controlled trial. Obstet Gynecol. 2007 Jan;109(1):20-7.

Helal A, Mashaly A, Amer T. Uterine artery occlusion for treatment of symptomatic uterine myomas. J Soc Laparoendosc Surg [Internet]. 2010 Jul [cited 2015 May 28];14(3):386-90. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3041036

Holub Z, Mara M, Eim J. Laparoscopic uterine artery occlusion versus uterine fibroid embolization. Int J Gynaecol Obstet. 2007;96(1):44-5.

HOPEFUL

Hirst A, Dutton S, Wu O, Briggs A, Edwards C, Waldenmaier L, et al. A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study. Health Technol Assess [Internet]. 2008 Mar;12(5):1-248. Available from: http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0006/64671/FullReport-hta12050.pdf

Dutton S, Hirst A, McPherson K, Nicholson T, Maresh M. A UK multicentre retrospective cohort study comparing hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids (HOPEFUL study): main results on medium-term safety and efficacy. BJOG. 2007 Nov;114(11):1340-51.

Ikink ME, Nijenhuis RJ, Verkooijen HM, Voogt MJ, Reuwer PJ, Smeets AJ, et al. Volumetric MR-guided high-intensity focused ultrasound versus uterine artery embolisation for treatment of symptomatic uterine fibroids: comparison of symptom improvement and reintervention rates. Eur Radiol. 2014 Oct;24(10):2649-57.

Iverson RE Jr, Chelmow D, Strohbehn K, Waldman L, Evantash EG. Relative morbidity of abdominal hysterectomy and myomectomy for management of uterine leiomyomas. Obstet Gynecol. 1996 Sep;88(3):415-9.

Manyonda IT, Bratby M, Horst JS, Banu N, Gorti M, Belli AM. Uterine artery embolization versus myomectomy: impact on quality of life--results of the FUME (Fibroids of the Uterus: Myomectomy versus Embolization) Trial. Cardiovasc Intervent Radiol. 2012 Jun;35(3):530-6.

Mara M, Kubinova K, Maskova J, Horak P, Belsan T, Kuzel D. Uterine artery embolization versus laparoscopic uterine artery occlusion: the outcomes of a prospective, nonrandomized clinical trial. Cardiovasc Intervent Radiol. 2012 Oct;35(5):1041-52.

Mara et al.

Mara M, Maskova J, Fucikova Z, Kuzel D, Belsan T, Sosna O. Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy. Cardiovasc Intervent Radiol [Internet]. 2008 Jan [cited 2015 May 28];31(1):73-85. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2700241

Mara M, Fucikova Z, Maskova J, Kuzel D, Haakova L. Uterine fibroid embolization versus myomectomy in women wishing to preserve fertility: preliminary results of a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2006 Jun 1;126(2):226-33.

Narayan A, Lee AS, Kuo GP, Powe N, Kim HS. Uterine artery embolization versus abdominal myomectomy: a long-term clinical outcome comparison. J Vasc Interv Radiol [Internet]. 2010 Jul [cited 2015 May 28];21(7):1011-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2900435

Odejinmi F, Maclaran K, Agarwal N. Laparoscopic treatment of uterine fibroids: a comparison of peri-operative outcomes in laparoscopic hysterectomy and myomectomy. Arch Gynecol Obstet. 2015 Mar;291(3):579-84.

Pinto I, Chimeno P, Romo A, Paul L, Haya J, de la Cal MA, et al. Uterine fibroids: uterine artery embolization versus abdominal hysterectomy for treatment--a prospective, randomized, and controlled clinical trial. Radiology [Internet]. 2003 Feb [cited 2015 May 28];226(2):425-31. Available from: http://pubs.rsna.org/doi/pdf/10.1148/radiol.2262011716

Razavi MK, Hwang G, Jahed A, Modanlou S, Chen B. Abdominal myomectomy versus uterine fibroid embolization in the treatment of symptomatic uterine leiomyomas. AJR Am J Roentgenol [Internet]. 2003 Jun [cited 2015 May 28];180(6):1571-5. Available from: http://www.ajronline.org/doi/pdf/10.2214/ajr.180.6.1801571

Ruuskanen A, Hippelainen M, Sipola P, Manninen H. Uterine artery embolisation versus hysterectomy for leiomyomas: primary and 2-year follow-up results of a randomised prospective clinical trial. Eur Radiol. 2010 Oct;20(10):2524-32.

Sawin SW, Pilevsky ND, Berlin JA, Barnhart KT. Comparability of perioperative morbidity between abdominal myomectomy and hysterectomy for women with uterine leiomyomas. Am J Obstet Gynecol. 2000 Dec;183(6):1448-55.

Siskin GP, Shlansky-Goldberg RD, Goodwin SC, Sterling K, Lipman JC, Nosher JL, et al. A prospective multicenter comparative study between myomectomy and uterine artery embolization with polyvinyl alcohol microspheres: long-term clinical outcomes in patients with symptomatic uterine fibroids. J Vasc Interv Radiol. 2006 Aug;17(8):1287-95.

Spies JB, Bradley LD, Guido R, Maxwell GL, Levine BA, Coyne K. Outcomes from leiomyoma therapies: comparison with normal controls. Obstet Gynecol. 2010 Sep;116(3):641-52.

Spies JB, Cooper JM, Worthington-Kirsch R, Lipman JC, Mills BB, Benenati JF. Outcome of uterine embolization and hysterectomy for leiomyomas: results of a multicenter study. Am J Obstet Gynecol. 2004;191(1):22-31.

Taran FA, Tempany CM, Regan L, Inbar Y, Revel A, Stewart EA, et al. Magnetic resonance-guided focused ultrasound (MRgFUS) compared with abdominal hysterectomy for treatment of uterine leiomyomas. Ultrasound Obstet Gynecol [Internet]. 2009 Nov [cited 2015 Sep 10];34(5):572-8. Available from: http://onlinelibrary.wiley.com/doi/10.1002/uog.7435/epdf

Appendix 4: Excluded Studies for Clinical Review

Irrelevant Study Design

Mettler L, Schollmeyer T, Lehmann-Willenbrock E, Dowaji J, Zavala A. Treatment of myomas by laparoscopic and laparotomic myomectomy and laparoscopic hysterectomy. Minim Invasive Ther Allied Technol. 2004 Feb;13(1):58-64.

Rabinovici J, David M, Fukunishi H, Morita Y, Gostout BS, Stewart EA, et al. Pregnancy outcome after magnetic resonance-guided focused ultrasound surgery (MRgFU) for conservative treatment of uterine fibroids. Fertil Steril. 2010 Jan;93(1):199-209.

Radosa MP, Owsianowski Z, Mothes A, Weisheit A, Vorwergk J, Asskaryar FA, et al. Long-term risk of fibroid recurrence after laparoscopic myomectomy. Eur J Obstet Gynecol Reprod Biol. 2014 Sep;180:35-9.

Volkers NA, Hehenkamp WJ, Birnie E, de Vries C, Holt C, Ankum WM, et al. Uterine artery embolization in the treatment of symptomatic uterine fibroid tumors (EMMY trial): periprocedural results and complications. J Vasc Interv Radiol. 2006 Mar;17(3):471-80.

Irrelevant Population

Aboulghar MM, Al-Inany HG, Aboulghar MA, Serour GI, Mansour RT. The effect of intramural fibroids on the outcome of IVF. Middle East Fertility Society Journal [Internet]. 2004 [cited 2015 Jun 2];9(3):263-7. Available from: http://www.bioline.org.br/pdf?mf04048

Calin D, Haradja H, Pacu I, Bratila E, Gheorghiu D, Rahimian H, et al. Laparoscopic myomectomy in infertility treatment. ARS Medica Tomitana. 2015;20(3):139-43.

Chong GO, Lee YH, Hong DG, Cho YL, Lee YS. Robotic hysterectomy or myomectomy without power morcellation: a single-port assisted three-incision technique with manual morcellation. Int J Med Robot. 2015 Jun 8. Epub ahead of print.

Iverson RE Jr, Chelmow D, Strohbehn K, Waldman L, Evantash EG, Aronson MP. Myomectomy fever: testing the dogma. Fertil Steril. 1999 Jul;72(1):104-8.

Lin JY, Lee WL, Wang PH, Lai MJ, Chang WH, Liu WM. Uterine artery occlusion and myomectomy for treatment of pregnant women with uterine leiomyomas who are undergoing cesarean section. J Obstet Gynaecol Res. 2010 Apr;36(2):284-90.

Mastrominas M, Pistofidis GA, Dimitropoulos K. Fertility outcome after outpatient hysteroscopic removal of endometrial polyps and submucous fibroids. J Am Assoc Gynecol Laparosc. 1996 Aug;3(4, Supplement):S29.

Shokeir T, El-Shafei M, Yousef H, Allam AF, Sadek E. RETRACTED: Submucous myomas and their implications in the pregnancy rates of patients with otherwise unexplained primary infertility undergoing hysteroscopic myomectomy: a randomized matched control study. Fertil Steril. 2010 Jul;94(2):724-9.

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Irrelevant Intervention

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Appendix 5: Clinical Evidence — Study Characteristics and patient baseline characteristics

Table 5-1: Study Characteristics — All Studies

Studies (First Author, Year, Country)	Study Design (Follow-Up Period)	Population (# in Each Arm and Total)	Intervention and Comparators	Key Outcomes
Myomectomy Versus Hysterectomy				
RCTs (no studies)				
Non-RCTs				
Odejinmi 2015, United Kingdom[13]	Retrospective cohort study. Choice of treatment was decided by the patient and surgeon.	Women undergoing laparoscopic MYO or HYS for UF. Exclusion: uterine size > 28 weeks or presence of > 10 fibroids in the MYO group. N = 400 – MYO 216 – HYS 184	Laparoscopic MYO Laparoscopic HYS	Peri-operative morbidity (including conversion to laparotomy, blood loss, blood transfusion, bladder injury, port site hernia and urinary retention)
Sawin 2000, United States[14]	Single-centre retrospective cohort study.	All women who underwent abdominal MYO and an equal number of women who underwent abdominal HYS. The procedure was the primary procedure and not incidental to a more involved operation. Exclusion: if the surgery involved a malignancy, pregnancy, gynecologic infection or performed on an emergency basis. N = 394 – MYO 197 – HYS 197	Abdominal MYO Abdominal HYS	Peri-operative morbidity (febrile morbidity, hemorrhage, unintended major surgical procedures, life-threatening events and rehospitalization).
Iverson 1996, United States[15]	Single-centre retrospective cohort study.	All women with hospital procedure codes for total abdominal HYS and MYO, from May 1988 through May 1993, were identified and included. Excluded: age > 45 years, surgery for conditions other than UF and intended vaginal HYS. N = 177 – MYO 103 – HYS 89	Abdominal MYO (vasopressin injection was used in 95% of MYO) Total abdominal HYS	Peri-procedural complications: blood loss, febrile morbidity, organ injuries.

Studies (First Author, Year, Country)	Study Design (Follow-Up Period)	Population (# in Each Arm and Total)	Intervention and Comparators	Key Outcomes
Uterine Artery Embolization Versus Hysterectomy				
RCTs				
Ruuskanen 2010, Finland[16]	Single-centre RCT, 2-year follow-up.	Symptomatic UF, severe enough to consider HYS. Exclusion: fertility preservation, myoma suitable for hysteroscopic MYO. N = 57 – MYO 27 (93% technical success) – HYS 30 (81% technical success)	UAE HYS (type and route of access were not standardized)	Symptom improvement, complications, re-interventions, and satisfaction.
Hehenkamp 2005 (EMMY), the Netherlands[17,38-40,65,66]	Multi-centre RCT, up to 5 years follow-up data after the primary intervention were presented.	Premenopausal women with symptomatic ultrasound-confirmed UF that were eligible for HYS Excluded: submucosal fibroids with 50% of diameter within the uterine cavity or dominant pedunculated serosal fibroids were present. N = 177 – UAE 88 (88.9% technical success) – HYS 89 (100% technical success)	UAE HYS via different routes (84% abdominal)	Menorrhagia after 2 years, complications, HRQoL (measured by SF-36, EQ-5D, HUI-3, UDI, IIQ, DDI, and SAQ), duration of hospital stay, re-intervention, patient satisfaction.
Pinto 2002, Spain[18]	Single-centre RCT, patients were followed up to 2 years.	Women with bleeding UF who were candidates for HYS. Excluded: women who wished to maintain fertility, UF > 10 cm in diameter. N=57 – UAE 38 (1 crossed over to HYS) – HYS 19 (3 crossed over to UAE)	UAE Abdominal HYS	Length of hospital stay, change in bleeding, change in dominant UF volume, complications, patient satisfaction.

Studies (First Author, Year, Country)	Study Design (Follow-Up Period)	Population (# in Each Arm and Total)	Intervention and Comparators	Key Outcomes
Non-RCTs				
Brochner 2009, Denmark[19]	Single-centre prospective study.	Women scheduled for HYS or UAE. The treatment was decided by the patient prior to inclusion in the study. Excluded: patients treated with steroids, with rheumatologic disease, diabetes, or ongoing malignant disease. N = 40 – UAE 20 – HYS 20	UAE Abdominal HYS	Inflammatory markers, patient satisfaction, hospital stay
Dutton 2007 (HOPEFUL), United Kingdom[20,46]	Multi-centre retrospective cohort study. The mean follow-up in the UAE groups was 4.6 years, and 8.6 years in the HYS group.	Women with symptomatic UFs and who received UAE from 1996 to 2002 or HYS from 1994 to 1995 in 18 UK NHS hospital trusts. No exclusions by age, other medical conditions or any other variables. N = 1,108 – UAE 649 – HYS 459	UAE HYS (total abdominal 86.7%)	Safety (severe, major, or minor complications), treatment effect (resolution of fibroid symptoms, patient satisfaction, further treatments for continuing or recurrent symptoms, pregnancy outcomes after UAE).
Spies 2004, United States[21]	Multi-centre prospective study, patients were followed up to 1 year.	Women aged ≥ 30 years and ≤ 50 years with symptomatic UF. Women in the UAE group would be excluded if they had submucosal UF with > 50% of their diameter within the uterine cavity or dominant pedunculated serosal UF. N = 152 – UAE 102 – HYS 50	UAE HYS via various routes	Change in bleeding (measured with a menorrhagia questionnaire, UAE arm only), change in other symptoms, general HRQoL (measured with SF-12), length of hospital stay, AEs, patient satisfaction.

Studies (First Author, Year, Country)	Study Design (Follow-Up Period)	Population (# in Each Arm and Total)	Intervention and Comparators	Key Outcomes
Uterine Artery Embolization Versus Myomectomy				
RCTs				
Manyonda 2012 (FUME), United Kingdom[22]	Single-centre RCT. Patients were followed for at least 1 year.	Premenopausal women with symptomatic UF and who desired uterine-preserving treatment, fibroid ≥ 4 cm in diameter. Exclusion: pedunculated fibroid, the fibroid mass extended beyond the level of umbilicus, were pregnant or actively planning or trying to conceive. N = 163 – UAE 82 (97% technical success), 8 withdrawals – MYO 81, 8 withdrawals	UAE Open abdominal MYO	HRQoL (measured by UFS-QOL), hospital stay, complications, and re-intervention.
Mara 2008, Czech Republic[23,67]	Single-centre RCT. Mean follow-up in the study was 24.9 months.	Age < 40 years, planned pregnancy, ultrasound-verified intramural UF of ≥ 4 cm. Exclusion: non-intramural localization of the main UF, UF of ≥ 12 cm by ultrasound or uterus greater than the 4th month of pregnancy by palpation, or with previous UF treatment (MYO, UAE or hormonal therapy). N = 121 – UAE 58 (89.7% technical success) – MYO 63 (92.1% technical success)	UAE Abdominal MYO, open or laparoscopy	Peri-procedural complications, early post-procedural (first 30 days after procedure) complications, and late post-procedural (> 30 days after procedure) complications; reproductive outcomes, re-intervention, symptom relief and length of hospital stay. The preliminary results from 63 patients in this study are not presented in this report.

Studies (First Author, Year, Country)	Study Design (Follow-Up Period)	Population (# in Each Arm and Total)	Intervention and Comparators	Key Outcomes
Non-RCTs				
Narayan 2010, United States[24]	Single-centre prospective cohort study. Patients were followed for at least 5 years	Women with symptomatic UF and received UAE or abdominal MYO. Patients were included if the procedure was performed 5 years prior to the study. N = 185 – UAE 87 – MYO 98	UAE Open abdominal MYO	Symptom evaluations (measured by SSS) and patient satisfaction.
Goodwin 2006, United States[25]	Multi-centre prospective cohort study. Treatment was assigned based on a best treatment decision made by the patient and physician as per the standard of care at each site. 6-month follow-up for both groups, and 1-year follow-up in UAE group only.	Age ≥ 30 years, ultrasound or MRI-confirmed symptomatic UF (severe enough to warrant therapy). Patients with a UFQoL score ≥ 90 at baseline was excluded unless she planned to undergo MYO for infertility. Patients with hysteroscopically resectable UFs were excluded. Patients in the UAE group would be excluded if they wished to become pregnant in the future. N = 209 – UAE 149 (using irregularly shaped particles: "Contour PVA Emboli") – MYO 60	UAE Abdominal MYO	Improvement in the UFQoL score from baseline to 6 months postoperatively, adverse events, overall HRQoL (instrument not specified), change in size of the dominant UF, uterine volume change, menstrual bleeding changes (with Ruta scale), and hospitalization days. Some outcomes (UFQoL, bleeding changes, AEs, pregnancies and fibroid treatments) were followed up to 1 year for UAE patients only.

Studies (First Author, Year, Country)	Study Design (Follow-Up Period)	Population (# in Each Arm and Total)	Intervention and Comparators	Key Outcomes
Siskin 2006, United States[26]	Multi-centre prospective cohort study. Treatment was assigned on the basis of treatment decisions made by the patients and physician according to the standard of care at each site. 6-month follow-up for MYO; 2-year follow-up for UAE.	Age ≥ 30 years, MRI-confirmed symptomatic UF, regular menstrual cycles, have not had any drug treatments for UF within 3 months of the procedure. Patients with a UFQoL score ≥ 90 at baseline was excluded unless she planned to undergo MYO for infertility. Patients in the UAE group would be excluded if they wished to become pregnant in the future, or had severe contrast agent allergy or pedunculated subserosal UF. N = 146 – UAE 77 (using spherical embolic agent: "Contour SE Microspheres") – MYO 69 This study was overlapped with the Goodwin 2006 study.[25] Most of the patients in the MYO group in the Siskin 2006 study[26] have been described in the Goodwin study. Patients in the UAE group were using a different embolic agent for embolization. The Siskin study had a longer follow-up period.	UAE Abdominal MYO	Improvement in the UFQoL score from baseline to 6 months postoperatively, AE, changes in tumour symptom scores, menorrhagia bleeding scores, change in uterine volume and UF size, additional treatment, and pregnancy. Some outcomes were measured at months 12 and 24.

Studies (First Author, Year, Country)	Study Design (Follow-Up Period)	Population (# in Each Arm and Total)	Intervention and Comparators	Key Outcomes
Razavi 2003, United States[27]	Single-centre retrospective study Mean follow-up time: UAE 14.3 months; MYO 14.6 months	Women with symptomatic UF and who had a strong desire to avoid HYS. N = 111 – UAE 67 – MYO 44	UAE Abdominal MYO	Successful symptom control (reporting category 5 or 6 in a scale), major AEs (leading to death, additional procedures, prolongation of hospital stay, any procedure-related undesirable outcome requiring treatment or clinic visits ≤ 30 days of the index procedure), and bleeding complications requiring nonautologous blood transfusion. Secondary outcomes: hospital stay and secondary interventions.
Broder 2002, United States[28]	Single-centre retrospective study Patients were surveyed 37 to 59 months after the primary procedure.	Women with symptomatic UF in one institution, and who underwent UAE or MYO. N = 81 – UAE 51 – MYO 30	UAE Abdominal MYO	Success or failure (required additional invasive treatment, no improvement or worsening of the overall symptoms score, or patient dissatisfaction) of the procedure at the time of survey, symptom improvement (using an investigator-developed scale), patient satisfaction, and re-intervention.

Studies (First Author, Year, Country)	Study Design (Follow-Up Period)	Population (# in Each Arm and Total)	Intervention and Comparators	Key Outcomes
Uterine Artery Embolization Versus Uterine Artery Occlusion				
RCTs				
Helal 2010, Egypt[29]	Single-centre RCT. Patients were followed for 1 year.	Premenopausal women with symptomatic UF and who did not desire further pregnancy. Excluded: subserous UF that could be easily removed by laparoscopic surgery, known adenomyosis, uterus size exceeded the umbilical level, submucous UF with a diameter of < 3.5 cm situated completely intracavitarily or with an intramural extension of > 50% N = 96 (90 received treatment) – UAE 45 – UAO 45	UAE UAO via laparoscopy	Menstrual blood loss, post-operative complications, and re-interventions.
Ambat 2009, India[30]	Single-centre RCT Patients were followed for 6 months.	Women with symptomatic UF; uteri size corresponded to 12 to 20 weeks of pregnancy. Excluded: had taken hormones during the last 3 months, and had suspected submucosal UFs, based on ultrasound scan. N = 20 – UAE 10 UAO 10	UAE UAO via laparoscopy	Menstrual blood loss (measured by PBAC score), reduction in uterine and UF volumes, AEs and complications (pain, measured by a visual analogue scale) following procedures.

Studies (First Author, Year, Country)	Study Design (Follow-Up Period)	Population (# in Each Arm and Total)	Intervention and Comparators	Key Outcomes
Cunningham 2008, United States[31]	Single-centre double-blind RCT (patient, the study gynecologist and the team performing the follow-up interviews were blinded),	Premenopausal women with ultrasound-confirmed UF and associated heavy uterine bleeding, and seeking UAE for the treatment; eligible participants should have no desire for fertility for the next 3 years or more; AMSS score ≥ 22; at least 1 UF, which was submucosal and > 3 cm in diameter, or more than 3 in number. Excluded: use of GnRH in the last 3 months N = 14 – UAE 8 – UAO 6	UAE UAO	Post-procedural pain, length of post-procedural institutional stay, bleeding symptoms (measured by AMSS)
Hald 2007, Norway[32,68]	Single-centre RCT 6 months and 48 months follow-up	Premenopausal women with symptomatic UF, and who did not want to have HYS. Excluded: uterus size exceeded the umbilical level, submucous myoma < 3.5 cm and was completely intracavitary or with an intramural extension of > 50%, and those who wished to have children. N=58 – UAE 29 – UAO 29	UAE UAO via laparoscopy	Reduction of blood loss from pre-treatment to 6 months postoperatively (using the PBAC), symptom reduction, postoperative pain, complications, secondary interventions, and clinical failure (defined as persisting symptoms requiring secondary treatment or no improvement at month 6).

Studies (First Author, Year, Country)	Study Design (Follow-Up Period)	Population (# in Each Arm and Total)	Intervention and Comparators	Key Outcomes
Non-RCTs				
Mara 2012, Czech Republic[33]	Single-centre prospective study. Treatment was chosen based on the patient's preferences. Mean length of follow-up was 45.5 months for the UAE group and 40.4 months for the UAO group.	Premenopausal women with symptomatic UF. UF ≥ 3 cm in diameter. Excluded: > 40 years, submucous myomas largely prominent into cavity, largely subserous or pedunculated myoma, predominantly cervical myoma, myoma with no perfusion or atypical pelvic tumour or of suspicious appearance. Preference for MYO or HYS, or myoma suited for laparoscopic MYO. N = 200 – UAE 100 (95% technical success) – UAO 100 (96% technical success)	UAE UAO via laparoscopy	Early post-procedural (first 30 days after procedure) complications including fever, infection, need for blood transfusion; late post-procedural (> 30 days after procedure) including uterine infection, requiring hormone replacement therapy, sudden severe uterine bleeding, emergent MYO or HYS, trans-cervical expulsion of myoma and uterine rupture; re-intervention; reproductive outcomes.
Holub 2006, Czech Republic[34]	Multi-centre prospective study. Follow-up period was unclear.	Inclusion/exclusion criteria NR. N = 295 – UAE 102 (14 patients conceived) – UAO 195 (20 patients conceived)	UAE UAO	Pregnancy outcomes
Myomectomy Versus Radiofrequency Thermal Ablation				
RCTs				
Brucker 2014,[37] **Hahn 2015,**[11] **Germany**	Single-centre RCT with non-inferiority design, margin 16.5 hours. Patients were blinded to the treatment assignment. Patients were followed for 1 year. 5 years' follow-up was planned.	Patients aged ≥ 18 years, had symptomatic UFs, uterine size ≤ 16 gestational weeks, UF < 10 cm in any diameter; desired uterine conservation. Excluded: high risk for or were known to have significant intra-abdominal adhesions, had taken any depot GnRH agonist ≤ 3 months prior to the screening, had pelvic radiation, cervical myoma; had UFs that were better treated via hysteroscopic methods. MYO was not performed on intramural myomas that were 1.0 to 1.5 cm in diameter, although this was not an exclusion criterion. N = 51 – MYO 25 – RFVTA 26 (1 patient did not receive allocated treatment and was excluded from analysis)	Laparoscopic MYO Laparoscopic RFVTA	Length of hospital stay, procedure-related complications, symptom improvement (measured by OTE and MIQ), HRQoL (measured by UFS-QOL, EQ-5D), re-intervention for UF, and pregnancy outcomes.

Studies (First Author, Year, Country)	Study Design (Follow-Up Period)	Population (# in Each Arm and Total)	Intervention and Comparators	Key Outcomes
Non-RCTs (no studies)				
Uterine Artery Embolization Versus Hysterectomy Versus Myomectomy				
RCTs (no studies)				
Non-RCTs				
Spies 2010, United States[12]	Multi-centre prospective study; patients were followed up to 1 year.	Premenopausal women aged ≥ 30 years and ≤ 50 years. Women in the UF treatment groups had to be scheduled to undergo HYS, MYO, or UAE. Women in the normal control group had no history of UF, and had normal gynecologic examination with regular menstrual cycle at enrolment. N = 375 – UAE 107 – HYS 106 – MYO 61 – Normal control 101	UAE HYS, various types MYO, various types Normal control	HRQoL measured by UFS-QOL and SF-36, length of hospital stay, AEs
Uterine Artery Embolization Versus MRgFU Ablation				
RCTs (no studies)				
Non-RCTs				
Ikink 2014, Netherlands[35]	Single-centre prospective study. Patients were followed up to 2 years.	Premenopausal women treated with MRgFU or UAE. UF size ≤ 12 cm and number ≤ 5. N = 119 – UAE 68 – MRgFU 51	UAE MRgFU	Symptom relief (measured by UFS-QOL), re-intervention.

Studies (First Author, Year, Country)	Study Design (Follow-Up Period)	Population (# in Each Arm and Total)	Intervention and Comparators	Key Outcomes
MRgFU Ablation Versus Hysterectomy				
RCTs (no studies)				
Non-RCTs				
Taran 2009, United States[36]	Multi-country (US, Israel, UK, and Germany) prospective study. Patients were followed up to 6 months.	Premenopausal women with symptomatic UF and treated with MRgFU or HYS. Aged ≥ 18 years and did not want children in the future. Raw SSS score ≥ 21. Multiple UFs were allowed for treatment of MRgFU. Excluded: UF size > 24 gestational weeks, positive pregnancy test and any contraindication to MRgFU or surgery. N = 192 – MRgFU 109 – HYS 83	MRgFU (most of the women had single UF) Total abdominal HYS (methods not specified)	HRQoL (measured by SF-36), safety.

AE = adverse event; AMSS = Aberdeen Menorrhagia Severity Scale (also known as Ruta Score); DDI = Defecation Distress Inventory; EQ-5D = EuroQol 5-Dimensions Questionnaire; GnRH = gonadotropin-releasing hormone; HRQoL = health-related quality of life; HYS = hysterectomy; IIQ = Incontinence Impact Questionnaire; MIQ = Menstrual Impact Questionnaires; MRgFU = magnetic resonance-guided focused ultrasound; MRI = magnetic resonance imaging; MYO = myomectomy; N = number of patients; OL = open-label; OTE = Overall Treatment Effect Survey; PBAC = Pictorial Blood Loss Assessment Chart; RCT = randomized controlled trial; RFVTA = radiofrequency volumetric thermal ablation; SAQ = the Sexual Activity Questionnaire; SF-36 = Short Form (36) Medical Outcome Survey; SSS = Symptom Severity Scale (of UFS-QOL; higher scores indicate more severe symptoms); UAE = uterine artery embolization; UAO = uterine artery occlusion; UDI = Urogenital Distress Inventory; UF = uterine fibroid; UFQoL = the Uterine Fibroid Quality of Life Questionnaire (a scale of 0 to 100; 100 indicates the best outcome, while 0 indicates the worst outcome); UFS-QOL = the Uterine Fibroid Symptom and Quality of Life questionnaire (consists of Symptom Severity scale and health-related quality of life questions. Higher scores in the former indicate greater symptom severity, while higher scores in the latter indicate better quality of life).

Table 5-2: Patient Baseline Characteristics (Myomectomy Versus Hysterectomy)

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/number)	Symptoms	Previous treatment, n (%)
RCTs (no studies)						
Non-RCTs						
Odejinmi 2015[13]						
MYO (n = 216)	38.0 ± 5.4	26.7 ± 5.0	0.54 ± 0.97	Uterine size (weeks): 14.1 ± 4.1	Menorrhagia: 43.0% Pain: 22.7% Pressure: 5.1% Infertility: 29.2%	C-section, MYO, or laparotomy: 30 (13.9%)
HYS (n = 184)	46.5 ± 4.5	30.5 ± 6.3	1.93 ± 1.37	Uterine size (weeks): 17.1 ± 5.9	Menorrhagia: 92.9% Pain: 3.8% Pressure: 3.3% Infertility: 0	C-section, MYO, or laparotomy: 24 (13.0%)
Spies 2010[12]						
MYO (n = 61)	40.6 ± 5.6	27.2 ± 6.7	Previous pregnancy: 36 patients (59.0%)	Uterus volume (mL): 430.86 ± SD 371.62 Number of UF: ≤ 5: 43 patients (70.5%) > 5: 18 patients (29.5%) Size of dominant UF (cm): 5.9 ± SD 3.3	NR	NR
HYS (n = 106)	44.5 ± 3.9	28.5 ± 7.4	Previous pregnancy: 92 patients (87.6%)	Uterus volume (mL): 549.44 ± SD 419.54 Number of UF: ≤ 5: 74 patients (69.8%) > 5: 25 patients (23.6%) Size of dominant UF (cm): 5.9 ± SD 3.1		
Sawin 2000[14]						
MYO (n =197)	36.1 ± 5.5	NR	0.5 ± SD 0.9	Uterine size: 14.4 ± SD 5.0 weeks	Bleeding: 35.6% Pain: 38.7%	GnRH agonists: 18 (9.1%) Previous MYO: 14 (7.1%)
HYS	43.9 ± 5.9	NR	1.6 ± SD	Uterine size: 15.6 ± SD	Bleeding: 122	GnRH

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/number)	Symptoms	Previous treatment, n (%)
(n = 197)			1.3	4.9 weeks	patients (61.9%) Pain: 61 patients (30.8%)	agonists: 20 (10.2%) Previous MYO: 23 (11.7%)
Iverson 1996[15]						
MYO (n = 103)	34.4	NR	Gravidity: 0.9 Parity: 0.2	Uterine size: 11.5 weeks Volume of dominant UF (mL): 193.2	Bleeding: 18 patients (17.5%) Pain or dysmenorrhea: 6 patients (5.8%)	GnRH agonist: 57 (55.3%)
HYS (n = 89)	39.2	NR	Gravidity: 1.8 Parity: 1.3	Uterine size: 15.2 weeks Volume of dominant UF (mL): 247.7	Bleeding: 44 patients (49.4%) Pain or dysmenorrhea: 10 patients (11.2%)	GnRH agonist: 21 (23.6%)

BMI = body mass index; C-section = Caesarean section; HYS = hysterectomy; MYO = myomectomy; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; UF = uterine fibroid.

Table 5-3: Patient Baseline Characteristics (Uterine Artery Embolization Versus Hysterectomy)

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/number)	Symptoms	Previous treatment (medical or surgical)
RCTs						
Ruuskanen 2010[16]						
UAE (n = 27)	48.5 ± 3.6	26.3 ± 6.0	1.9 ± 0.9	Number of UF: 1: 2 patients (8%) 2 to 4: 12 patients (44%) ≥ 5: 13 patients (48%) Uterus volume (mL): 422 ± SD 242 Dominant UF volume (mL): 131 ± 149 Location of UF: - Intramural: 23 patients (85%) - Submucosal: 1 patient (4%) - Subserosal: 3 patients (11%)	Menorrhagia: – 18 (67%) Pain: – 7 (26%) Urinary symptoms: – 20 (74%) Anemia: – 10 (37%) Pressure symptoms: – 20 (74%)	Hormonal treatment: 13 (48.1%) MYO: 2 (10%)
HYS (n = 30)	48.3 ± 3.9	26.5 ± 4.3	1.7 ± 1.0	Number of UF: 1: 4 patients (13%) 2 to 4: 12 patients (40%) ≥ 5: 14 patients (47%) Uterus volume (mL): 438 ± SD 308 Dominant UF volume (mL): 138 ± 161 Location of UF: - Intramural: 19 patients (63%) - Submucosal: 5 patients (17%) - Subserosal: 6 patients (20%)	Menorrhagia: – 25 (83%) – Pain: – 16 (53%) Urinary symptoms: – 26 (87%) Anemia: – 13 (43%) Pressure symptoms: – 26 (87%)	Hormonal treatment: 18 (60%) MYO: 3 (7%)

Studies (First Author, Year)	Demographic Characteristics			Demographic Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/number)	Symptoms	Previous treatment (medical or surgical)
Hehenkamp 2005 (EMMY)[38]						
UAE (n = 88)	44.6 ± 4.8	26.7 ± 5.6	0: 30 (34.1%) ≥ 1: 58 (65.9%)	Uterine volume (cm^3, median [range]): 321 (31 to 3,005) Number of UF (median [range]): 2 (1-20) UF volume (cm^3, median [range]): 59 (1 to 673)	-Menorrhagia: 88 (100%) -Pain: 15 (17.0%) -Urinary symptoms: 13 (14.8%) -Anemia: 43 (48.9%) -Pressure symptoms: 23 (26.1%)	-No treatment: 11 (12.5%) -Hormonal: 59 (67.0%) -NSAIDs or tranexamic acid: 45 (51.1%) -Iron supplement or blood transfusion: 50 (56.8%) -Surgical procedures: 17 (19.3%)
HYS (n = 89)	45.4 ± 4.2	25.4 ± 4.0	0: 20 (22.5%) ≥ 1: 69 (77.5%)	Uterine volume (cm^3, median [range]): 313 (58 to 3,617) Number of UF (median [range]): 2 (1 to 9) UF volume (cm^3, median [range]): 87 (4 to 1,641)	-Menorrhagia: 89 (100%) -Pain: 14 (15.7%) -Urinary symptoms: 20 (22.5%) -Anemia: 42 (47.2%) -Pressure symptoms: 25 (28.1%)	-No treatment: 15 (16.9%) -Hormonal: 59 (66.3%) -NSAIDs or tranexamic acid: 45 (51.1%) -Iron supplement or blood transfusion: 50 (56.8%) -Surgical procedures: 17 (19.3%)

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/number)	Symptoms	Previous treatment (medical or surgical)
Pinto 2002[18]						
UAE (n = 38)	46.4 ± 4.4	NR	Previous pregnancy: 2.6 ± SD 1.2	Number of UF: 1.6 ± SD 0.5 Location of UF: - Intramural: 16 patients (42%) - Submucosal: 15 patients (40%) - Subserous: 7 patients (18%) UF volume (cm^3): 72.0 ± SD 86	Menorrhagia: 37 patients (97%) Metrorrhagia: 19 patients (50%)	None: 23 (61%) Hormonal: 14 (37%) MYO: 1 (3%)
HYS (n = 19)	44.6 ± 5.0		Previous pregnancy: 3.2 ± SD 1.8	Number of UF: 1.6 ± SD 0.5 Location of UF: - Intramural: 13 patients (68%) - Submucosal: 2 patients (11%) - Subserous: 4 patients (21%) UF volume (cm^3): 113 ± SD 138	Menorrhagia: 17 patients (90%) Metrorrhagia: 9 patients (47%)	None: 9 (47%) Hormonal: 10 (53%) MYO: 0
Non-RCTs						
Spies 2010[12]						
UAE (n = 107)	43.2 ± 3.7	28.4 ± 6.5	Previous pregnancy: 77 (73.3%)	Uterus volume (mL): 579.54 ± SD 339.85 Number of UF: ≤ 5: 63 patients (58.9%) > 5: 42 patients (39.3%) Size of dominant UF (cm): 6.0 ± SD 2.3	NR	NR
HYS (n = 106)	44.5 ± 3.9	28.5 ± 7.4	Previous pregnancy: 92 (87.6%)	Uterus volume (mL): 549.44 ± SD 419.54 Number of UF: ≤ 5: 74 patients (69.8%) > 5: 25 patients (23.6%) Size of dominant UF (cm): 5.9 ± SD 3.1		

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/number)	Symptoms	Previous treatment (medical or surgical)
Brochner 2009[19]						
UAE (n = 20)	The 2 groups were comparable in age, BMI, and comorbidity. Data were not provided		NR	Average number of UF: 1.8 Average diameter of UF: 6.8 cm	NR	NR
HYS (n = 20)				Average number of UF: 1.6 Average diameter of UF: 7.5 cm		
Dutton 2007 (HOPEFUL)[20,46]						
UAE (n = 649)	43.8 ± 6.5	26.5 ± 5.5	Nulliparous: 296 (45.6%) Multiparous: 328 (50.5%) Missing: 25 (3.9%)	Number of UF: 1 to 3: 155 patients (23.9%) > 3: 97 patients (14.9%) Volume of dominant UF (cm^3): 330.1 ± SD 379.2 Maximum diameter of dominant UF (cm): 8.5 ± 3.5 Location of UF: - Submucosal: 44 patients (6.8%) - Intramural: 130 (20.0%) - Subserosal: 26 patients (4.0%) - Pedunculated: 6 (0.9%) - Missing: 443 (68.3%)	Menstrual only: 133 (20.5%) Bulk only: 72 (11.1%) Both: 384 (59.2%)	Pelvic surgery: 169 (26.0%)
HYS (n = 459)	46.5 ± 6.8	26.7 ± 4.9	Nulliparous: 65 (14.2%) Multiparous: 391 (85.2%) Missing: 3 (0.6%)	Number of UF: 1 to 3: 94 patients (20.5%) > 3: 50 patients (10.9%) Volume of dominant UF (cm^3): 289.0 ± SD 400.6 Maximum diameter of dominant UF (cm): 6.5 ± 3.9 Location of UF: - Submucosal: 10 patients (2.2%) - Intramural: 44 (9.6%) - Subserosal: 12 patients (2.6%) - Pedunculated: 12 (2.6%) - Missing: 381 (83.0%)	Menstrual only: 173 (37.7%) Bulk only: 59 (12.9%) Both: 165 (35.9%)	Pelvic surgery: 65 (14.2%)

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/number)	Symptoms	Previous treatment (medical or surgical)
Spies 2004[21]						
UAE (n = 102)	42.6 ± 4.0	NR	Previous pregnancy: 0: 19 (19%) ≥ 1: 83 (81%)	Uterus volume (mL): 689.4 ± SD 466.1 Number of UF: 1: 27 patients (26%) > 1: 75 patients (73%) Size of dominant UF (mL): 146.8 ± SD 158.5 Location of UF: - Intramural: 61 patients (60%) - Subserosal: 19 patients (19%) - Submucosal: 17 patients (17%) - Transmural: 11 patients (11%) - Pedunculated: 2 patients (2%)	Self-assessment of menstrual flow: Extremely or moderately heavy: 98 (96%) UF-related pain: 94 (93%) UF-related discomfort: 98 (97%) Urinary dysfunction: 93 (92%)	None: 53 (52%) Hormonal: 39 (39%) Invasive: 53 (53%)
HYS (n = 50)	41.6 ± 5.3		Previous pregnancy: 0: 8 (16%) ≥ 1: 42 (84%)	Uterus volume (mL): 389.2 ± SD 521.2 Number of UF: 1: 20 patients (40%) > 1: 29 patients (58%) Size of dominant UF (mL): 90.6 ± SD 354.8 Location of UF: - Intramural: 32 patients (64%) - Subserosal: 8 patients (16%) - Submucosal: 13 patients (26%) - Transmural: 1 patient (2%) - Pedunculated: 4 patients (8%)	Self-assessment of menstrual flow: Extremely or moderately heavy: 42 (84%) UF-related pain: 47 (96%) UF-related discomfort: 44 (90%) Urinary dysfunction: 41 (84%)	None: 35 (70%) Hormonal: 12 (24%) Invasive: 10 (20%)

BMI = body mass index; HYS = hysterectomy; MYO = myomectomy; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; SD = standard deviation; UAE = uterine artery embolization; UF = uterine fibroid.

Table 5-4: Patient Baseline Characteristics (Uterine Artery Embolization Versus Myomectomy)

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year (mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/ number)	Symptoms	Previous treatment
RCTs						
Manyonda 2012[22]						
UAE (n = 74)	44 ± 5.7	NR	NR	Size of dominant fibroid (cm): 7.7 ± SD 3.8 Uterine volume (mL): 973 ± SD 946.8	UFS-QOL: -Symptom Severity Score: 59.8 ± SD 22.1 -Total HRQL: 40.2 ± SD 23.1	NR
MYO (n = 73)	43.2 ± 5.3			Size of dominant fibroid (cm): 6.5 ± SD 2.8 Uterine volume (mL): 707.1 ± SD 511.8	UFS-QOL: -Symptom Severity Score: 55.9 ± SD 21.2 -Total HRQL: 46.4 ± SD 22.5	
Mara 2008[23]						
UAE (n = 58)	32.4	NR	Sterile: 11 patients (19.0%)	Size of dominant fibroid (mm): 62.3 ± SD 19.1 Number of UF: 1: 39 (67.2%) ≥ 2: 19 (32.8%)	110 (90.9%) were symptomatic. No details were provided.	Previous UF treatment not allowed
MYO (n = 63)	32.0		Sterile: 24 patients (38.1%)	Size of dominant fibroid (mm): 59.8 ± SD 16.5 Number of UF: 1: 40 (63.5%) ≥ 2: 23 (36.5%)		Previous UF treatment not allowed

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year (mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/number)	Symptoms	Previous treatment
Non-RCTs						
Spies 2010[12]						
UAE (n = 107)	43.2 ± 3.7	28.4 ± 6.5	Previous pregnancy: 77 (73.3%)	Uterus volume (mL): 579.54 ± SD 339.85 Number of UF: ≤ 5: 63 patients (58.9%) > 5: 42 patients (39.3%) Size of dominant UF (cm): 6.0 ± SD 2.3	NR	NR
MYO (n = 61)	40.6 ± 5.6	27.2 ± 6.7	Previous pregnancy: 36 (59.0%)	Uterus volume (mL): 430.86 ± SD 371.62 Number of UF: ≤ 5: 43 patients (70.5%) > 5: 18 patients (29.5%) Size of dominant UF (cm): 5.9 ± SD 3.3		
Narayan 2010[24]						
UAE (n = 87)	42.9 ± 7.8	NR	0.8 ± 0.9	NR	SSS score: 53.6 (95% CI, 44.9 to 62.4)	History of medication use: 25 (29.2%)
MYO (n = 98)	37.7 ± 5.8		0.4 ± 0.6		SSS score: 48.6 (95% CI, 40.7 to 56.4)	History of medication use: 62 (63.4%)

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year (mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/ number)	Symptoms	Previous treatment
Goodwin 2006[25]						
UAE (n = 149)	43.9, SD NR	NR	Previous pregnancy: 75.2%	Uterine volume (cm^3): 658.4 Number of UF: ≤ 5: 47 (31.5%) > 5: 102 (68.5%) Size of dominant fibroid (cm^3, mean ± SD): 182.1 ± 209.0 Location: -Intramural: 88 (59.1%) -Submucosal and submucosal pedunculated: 18 (12.1%) -Subserosal and subserosal pedunculated: 39 (26.2%)	Abnormal bleeding: 77 (51.7%) Bulk or pressure: 38 (25.5%) Pelvic pain: 29 (19.5%)	NR
MYO (n = 60)	38.2, SD NR		Previous pregnancy: 48.3%	Uterine volume (cm^3): 590.6 Number of UF: ≤ 5: 27 (45.0%) > 5: 27 (45.0%) Missing: 6 (10.0%) Size of dominant fibroid (cm^3, mean ± SD): 226.9 ± 196.4 Location: -Intramural: 26 (43.3%) -Submucosal and submucosal pedunculated: 5 (8.3%) -Subserosal and subserosal pedunculated: 21 (35.0%)	Abnormal bleeding: 20 (33.3%) Bulk or pressure: 16 (26.7%) Pelvic pain: 18 (30%)	

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year (mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/number)	Symptoms	Previous treatment
Siskin 2006[26]						
UAE (n = 77)	43.9, SD NR	NR	Previous pregnancy: 80.5%	Uterine volume (cm^3): 706.4 (range 134 to 3,101) Number of UF: ≤ 5: 19 (24.7%) > 5: 54 (70.2%) Missing: 4 (5.2%) Size of dominant fibroid (cm^3): 134.84 ± SD 159.91 Location: -Intramural: 45 (58.4%) -Submucosal and submucosal pedunculated: 12 (15.6%) -Subserosal and subserosal pedunculated: 15 (19.5%)	Abnormal bleeding: 53 (68.8%) Bulk or pressure: 11 (13.4%) Pelvic pain: 12 (15.6%)	NR
MYO (n = 69)	37.8, SD NR		Previous pregnancy: 50.7%	Uterine volume (cm^3): 618.0 (range 99.9 to 2,131) Number of UF: ≤ 5: 32 (46.2%) > 5: 31 (44.9%) Missing: 6 (8.7%) Size of dominant fibroid (cm^3): 230.30 ± SD 192.62 Location: Intramural: 32 (46.4%) Submucosal and submucosal pedunculated: 5 (7.2%) Subserosal and subserosal pedunculated: 24 (34.8%)	Abnormal bleeding: 21 (30.4%) Bulk or pressure: 20 (29.0%) Pelvic pain: 21 (30.4%)	

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year (mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/ number)	Symptoms	Previous treatment
Razavi 2003[27]						
UAE (n = 67)	44.2 (range 31 to 56)	NR	NR	NR	Bleeding: 52/62 (84%) Pelvic pain: 34/62 (55%) Mass effect: 37/62 (60%)	NR
MYO (n = 44)	37.7 (range 28 to 28)				Menorrhagia: 22/40 (55%) Pelvic pain: 26/40 (65%) Mass effect: 23/40 (58%)	
Broder 2002[28]						
UAE (n = 51)	43.5 (range 27 to 66)	NR	NR	NR	Menorrhagia: 40 (78%) Abdominal or pelvic pain: 20 (39%) Overall symptom score: 13 (range 6 to 28)	Hormonal: 13 (25%) All had prior surgery. Prior MYO: 40 (78%)
MYO (n = 30)	37.6 (range 28 to 45)				Menorrhagia: 25 (83%) Abdominal or pelvic pain: 19 (63%) Overall symptom score: 15 (range 9 to 29)	Hormonal: 9 (30%) MYO: 1 (3%)

CI = confidence interval; HRQL = sum of the health-related quality of life subscales in the UFS-QOL (higher scores indicate better quality of life); MYO = myomectomy; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SSS = Symptom Severity Scale (of UFS-QOL); UAE = uterine artery embolization; UF = uterine fibroid; UFS-QOL = Uterine Fibroid Symptom and Quality of Life Questionnaire.

Table 5-5: Patient Baseline Characteristics (Uterine Artery Embolization Versus Uterine Artery Occlusion)

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2 (median, range)	Parity	Diagnosis (UF location/size/ number)	Symptoms	Previous treatment, n (%)
RCTs						
Helal 2010[29]						
UAE (n = 45) UAO (n = 45)	The study indicated that the 2 groups were similar with respect to age, BMI, and parity and baseline symptom. Data were not reported.			NR	The study indicated that the 2 groups were similar in baseline symptom. Data were not reported.	NR
Ambat 2009[30]						
UAE (n = 10)	40.8	NR	2.4 ± SD 1.4	Dominant UF was intramural in all. Multiple UF: 9 patients (90%) UF volume (mL): 58.0 Uterine volume (mL): 222.7	-Menorrhagia: 10 (100%) -Dysmenorrhea: 2 (20%) -Bulk-related symptoms: 1 (10%) -PBAC score: 267.3	NR
UAO (n = 10)	40.5		2.9 ± SD 1.0	Dominant UF was intramural in all. Multiple UF: 7 patients (70%) UF volume (mL): 38.4 Uterine volume (mL): 224.7	-Menorrhagia: 10 (100%) -Dysmenorrhea: 7 (70%) -Bulk-related symptoms: 1 (10%) -PBAC score: 444.9	
Cunningham 2008[31]						
UAE (n = 8)	46.5 (range 35 to 53)	NR	NR	Uterine volume (cm^3): 557.3 (range 225 to 1,133)	AMSS score: 53 (range 51.1 to 76.7)	NR
UAO (n = 6)	47.5 (range 37 to 53)			Uterine volume (cm^3): 612.4 (range 225 to 1,133)	AMSS score: 54 (range 51.1 to 69.8)	

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2 (median, range)	Parity	Diagnosis (UF location/size/ number)	Symptoms	Previous treatment, n (%)
Hald 2007[32]						
UAE (n = 29)	42.5 ± 4.3	23.0 (19.3 to 37.3)	Nullipara: 11 (37.9%)	-Uterine volume (mL): 598 (171 to 1,276) -Size of dominant UF (mL): 257 (35 to 530) -Submucous, subserous, or transmural UF: 6/3/20 patients	-Menorrhagia: 29 (100%) PBAC score: 358 (63 to 1,257) -Bulk symptoms: 24 (82.8%) -Hemoglobin (g/100 mL): 11.6 ± 1.5	NR
UAO (n = 29)	43.3 ± 5.2	23.5 (20.2-39.2)	Nullipara: 11 (37.9%)	-Uterine volume (mL): 557 (128 to 1,921) -Size of dominant UF (mL): 137 (6 to 847) -Submucous, subserous, or transmural UF: 6/6/17 patients	-Menorrhagia: 28 (96.6%) -PBAC score: 317 (108 to 1,200) -Bulk symptoms: 20 (69.0%) -Hemoglobin (g/100 mL): 11.7 ± 1.6	
Non-RCTs						
Mara 2012, Czech Republic[33]						
UAE (n = 100)	33.1 ± 3.7	25.2 ± 5.0	NR	Number of UF: 2.4 ± 2.4 Size of dominant UF (mm): 68.2 ± SD 18.2 Volume of dominant UF: 188.7 ± SD 39.6	NR	NR
UAO (n = 100)	34.9 ± 4.0	23.4 ± 3.5		Number of UF: 2.3 ± 1.4 Size of dominant UF (mm): 48.3 ± SD 11.1		

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2 (median, range)	Parity	Diagnosis (UF location/size/ number)	Symptoms	Previous treatment, n (%)
				Volume of dominant UF: 59.9 ± SD 41.2		
Holub 2006, Czech Republic[34]						
UAE (n = 14 conceived)	NR					
UAO (n = 20 conceived)						

AMSS = Aberdeen Menorrhagia Severity Scale; BMI = body mass index; HYS = hysterectomy; MYO = myomectomy; NR = not reported; PBAC = Pictorial Bleeding Assessment Chart; RCT = randomized controlled trial; SD = standard deviation; UAE = uterine artery embolization; UAO = uterine artery occlusion; UF = uterine fibroid.

Table 5-6: Patient Baseline Characteristics (Uterine Artery Embolization Versus MRgFU)

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/ number)	Symptoms	Previous treatment
RCTs (no studies)						
Non-RCTs						
Ikink 2014[35]						
UAE (n = 68)	43 (IQR 41 to 46)	NR	NR	Number of UF: 1: 23 patients (34%) > 1: 45 patients (66%) Dominant UF volume (cm^3): 166 (IQR 65 to 236) Maximum diameter of dominant UF (cm): 7.2 (IQR 5.5 to 8.4) Uterus volume (cm^3): 486 (IQR 347-689) Location of UF: - Intramural: 38 patients (56%) - Subserosal: 8 (12%) - Submucosal: 22 patients (32%)	Menorrhagia: 63 (93%) Bulky symptoms: 50 (74%) Pain: 31 (46%) UFS-QOL: - tSSS: 65.3 (IQR 56.3 to 74.2) - Total HRQoL: 48.5 (IQR 33.8-65.1)	NR

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/ number)	Symptoms	Previous treatment
MRgFU (n = 51)	46 (IQR 43 to 49)			Number of UF: 1: 12 patients (24%) > 1: 39 patients (76%) Dominant UF volume (cm^3): 273 (IQR 142 to 478) Maximum diameter of dominant UF (cm): 8.5 (IQR 6.5 to 10.7) Uterus volume (cm^3): 792 (IQR 454 to 1,104) Location of UF: - Intramural: 30 patients (59%) - Subserosal: 13 (25%) - Submucosal: 8 patients (16%)	Menorrhagia: 37 (73%) Bulky symptoms: 47 (92%) Pain: 36 (71%) UFS-QOL: - tSSS: 53.1 (IQR 40.6 to 68.8) - Total HRQoL: 60.3 (IQR 40.4 to 81.0)	

BMI = body mass index; HRQoL = health-related quality of life; IQR = interquartile range; MRgFU = magnetic resonance-guided focused ultrasound; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; tSSS = transformed Symptom Severity Score (higher scores indicate more severe symptoms); UAE = uterine artery embolization; UF = uterine fibroid; UFS-QOL = Uterine Fibroid Symptom and Quality of Life Questionnaire.

Table 5-7: Patient Baseline Characteristics (MRgFU Versus Hysterectomy)

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year (mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/number)	Symptoms	Previous treatment
RCTs (no studies)						
Non-RCTs						
Taran 2009[36]						
MRgFU (n = 109)	44.8 ± 4.9	25.8 ± 5.2	NR	Most of the women were treated for single UF. Other details NR.	UFS-QOL: - SSS: 61.7 ± 15.2 - Total HRQoL: 47.0±18.6	None: 76 (70%) NSAIDs, Depo-Provera, or oral progesterone: 24 (23%)
HYS (n = 83)	44.4 ± 5.6	29.9 ± 6.0		NR	UFS-QOL: - SSS: 69.6 ± 8.1 - Total HRQoL: 38.4 ± 23.8	None: 35 (42%) NSAIDs, Depo-Provera, oral progesterone: 44 (53%)

BMI = body mass index; HRQoL = health-related quality of life; HYS = hysterectomy; MRgFU = magnetic resonance-guided focused ultrasound; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; SD = standard deviation; SSS = Symptom Severity Score (transformed; higher scores indicate more severe symptoms); UF = uterine fibroid; UFS-QOL = the Uterine Fibroid Symptom and Quality of Life Questionnaire.

Table 5-8: Patient Baseline Characteristics (Myomectomy Versus RFVTA)

Studies (First Author, Year)	Demographic Characteristics			Disease Characteristics		
	Age, year ((mean ± SD)	BMI, kg/m^2	Parity	Diagnosis (UF location/size/number)	Symptoms	Previous treatment
RCTs						
Brucker 2014,[37] Hahn 2015[11]						
MYO (n = 25)	34.4 ± 6.1	24.0	NR	Number of UF: 2.4 ± SD 1.6 Diameter of dominant UF (cm): 9.2 Location of UF: - Submucosal: 2 patients (3.3%) - Transmural: 3 patients (4.9%) - Intramural: 26 patients (42.6%) - Intramural UF abutting the endometrium: 0 - Subserosal: 34 (55.7%) - Pedunculated subserosal: 2 (3.3%)	Heavy menstrual bleeding: 18 (72%) Pelvic discomfort or pain: 6 (24%) UFS-QOL -Symptom Severity Subscale score: 41.8 -Quality of life subscale score: 70.2	NR
RFVTA (n = 25)	40.0 ± 7.8	22.6		Number of UF: 2.9 ± SD 2.6 Diameter of dominant UF (cm): 8.7 Location of UF: - Submucosal: 0 - Transmural: 0 - Intramural: 33 patients (45.8%) - Intramural UF abutting the endometrium: 2 (2.8%) - Subserosal: 37 (51.4%) - pedunculated subserosal: 0	Heavy menstrual bleeding: 21 (84%) Pelvic discomfort or pain: 3 (12%) UFS-QOL -Symptom Severity Subscale score: 39.9 -Quality of life subscale score: 77.2	
Non-RCTs (no studies)						

BMI = body mass index; MYO = myomectomy; NR = not reported; RCT = randomized controlled trial; RFVTA = radiofrequency volumetric thermal ablation; SD = standard deviation; UF = uterine fibroid; UFS-QOL = the Uterine Fibroid Symptom and Quality of Life questionnaire (consists of Symptom Severity scale and health-related quality of life questions. Higher scores in the former indicate greater symptom severity, while higher scores in the latter indicate better quality of life).

Appendix 6: Clinical Evidence — Critical Appraisal of Studies

First Author, Publication Year, Country	Strengths	Limitations
Randomized controlled trials		
Brucker 2014, Germany[37]	• Patients were blinded • Interventions and outcomes were described • Loss to follow-up was reported • Power calculation was conducted • COI was reported	• Unclear whether the participants were representative of the entire population • Analysis was based on the patients who received allocated intervention
Manyonda 2012, United Kingdom[22]	• Interventions and outcomes were described • Loss to follow-up was reported • ITT analysis was performed • Power calculation was conducted • COI was reported	• Unclear whether the participants were representative of the entire population
Helal 2010, Egypt[29]	• Interventions and outcomes were described • Power calculation was performed • All patients completed the study; none lost to follow-up	• Unclear whether the randomization was conducted appropriately • Unclear whether the participants were representative of the entire population • Unclear whether ITT analysis was performed • Results were insufficiently reported; e.g., complications • COI was not reported
Ruuskanen 2010, Finland[16]	• Interventions and outcomes were described • Loss to follow-up was reported • ITT analysis was performed • Funding source was reported	• Unclear whether the randomization was conducted appropriately • Power calculation was not conducted • Unclear whether the participants were representative of the entire population
Ambat 2009, India[30]	• Computer-generated random number sequence used for randomization • Interventions and outcomes were described	• No power calculation; 20 patients were enrolled in this study • Unclear whether the participants were representative of the entire population • Unclear whether ITT analysis was performed • Loss to follow-up was not reported • COI was not reported
Cunningham 2008, United States[31]	• Interventions and outcomes were described • Loss to follow-up was reported • COI was reported	• Unclear whether the randomization was conducted appropriately • Power calculation was not conducted • Unclear whether ITT analysis was performed • Only preliminary results were available
Mara 2008, Czech Republic[23]	• Interventions and outcomes were described • Loss to follow-up was reported • ITT analysis was performed • Funding source was reported	• Power calculation was not conducted • Unclear whether the participants were representative of the entire population
Hald 2007, Norway[32]	• Interventions and outcomes were described • Loss to follow-up was reported • Both ITT and per-protocol analysis were performed • Power calculation was conducted	• Unclear whether the participants were representative of the entire population • The study had no sufficient power to detect between-group differences • Funding source was not reported

First Author, Publication Year, Country	Strengths	Limitations
Hehenkamp 2005, Netherlands[17]	• Interventions and outcomes were described • Loss to follow-up was reported • Power calculation was conducted • ITT analysis was performed • Funding source was reported	• Unclear whether the participants were representative of the entire population
Pinto 2002, Spain[18]	• Interventions and outcomes were described • Power calculation was performed	• Data on most of the outcomes were analyzed based on the treatment that patient actually received • COI was not reported
Non-randomized controlled trials		
Odejinmi 2015, United States[13]	• Interventions and outcomes were described • COI was reported	• Unclear whether patients in different intervention groups were recruited over the same period of time • Treatment was self-selected by the patient and physician • Baseline patient characteristics differed between groups and the differences were not adjusted for in the analysis • Sample size determination was not reported • Unclear whether the participants were representative of the entire population
Ikink 2014, Netherlands[35]	• Interventions and outcomes were described • Potential confounders were identified a priori and adjusted for in analysis • Loss to follow-up was reported • COI was reported	• Patients in different intervention groups were recruited from different sites; unclear whether patients were recruited over the same period of time • Sample size determination was not described • Imbalanced baseline patient characteristics between groups • Unclear whether the participants were representative of the entire population
Mara 2012, Czech Republic[33]	• Prospective study • Patients were enrolled over same period of time • Interventions and outcomes were described • COI was reported	• Treatment was chosen based on patient's preferences • Sample size determination was not reported • Imbalanced baseline patient characteristics between groups and the differences were not adjusted for in the analysis • Unclear whether the participants were representative of the entire population
Narayan 2010, United States[24]	• Interventions and outcomes were described • Potential confounders were identified a priori and adjusted for in analysis • Missing data imputation was performed • Long-term data (≥ 5 years) were available	• Unclear whether patients in different intervention groups were recruited over the same period of time • Treatment was self-selected by the patients • Some baseline patient characteristics were not comparable between groups • Per-protocol analysis was performed • Unclear whether the participants were representative of the entire population • Funding source was not reported
Spies 2010, United States[12]	• Prospective study	• Unclear whether patients in different

First Author, Publication Year, Country	Strengths	Limitations
	• Loss to follow-up was reported • Sample size determination was reported • Funding source was reported	intervention groups were recruited over the same period of time • No descriptions on interventions • Treatment was self-selected by the patients • Some baseline patient characteristics were not comparable between groups • Per-protocol analysis was performed • Unclear whether the participants were representative of the entire population
Brochner 2009, Denmark[19]	• Prospective study • Patients were enrolled over same period of time • Interventions and outcomes were described • COI was reported	• Treatment selection was made by the patients • Sample size determination was not reported • Baseline patient characteristics were not reported in detail • Results were reported graphically, or briefly described with no *P* values provided • Unclear whether the participants were representative of the entire population
Taran 2009, United States[36]	• Prospective multi-country study • Women who underwent MRgFU or hysterectomy were recruited from different medical centres, to avoid referral bias between groups • Patients were enrolled over the same period of time	• Baseline patient characteristics differed between groups • Sample size determination was not reported • Some key baseline patient characteristics were not reported, such as the uterine fibroid size and location, and dominant symptoms • Unclear if the participants were representative of the entire population • COI was not reported
Dutton 2007, United Kingdom[20]	• Large clinical study with long-term effectiveness and safety data • Interventions and outcomes were described • Potential confounders were identified a priori • Missing data were estimated using various methods • Sample size determination was described • Funding source was reported	• Patients in different intervention groups were recruited over the different period of time • Some baseline patient characteristics were not comparable between groups
Goodwin 2006, United States[25]	• Prospective study • Patients were enrolled over the same period of time • Interventions and outcomes were described • Independent committee assisted in interpreting the results • Funding source was reported	• Treatment was selected by patients and physicians according to the standard of care at the respective site • Sample size determination was not reported • Imbalanced baseline patient characteristics between groups • Unclear whether the participants were representative of the entire population
Siskin 2006, United States[26]	• Prospective study • Patients were enrolled over the same period of time • Interventions and outcomes were described	• Sample size determination was not reported • Imbalanced baseline patient characteristics between groups • Unclear whether the participants were

First Author, Publication Year, Country	Strengths	Limitations
	• An independent committee was responsible for reviewing the adverse events • All images were evaluated by a central core laboratory • Funding source was reported	representative of the entire population
Holub 2006, Czech Republic[34]	• Prospective study	• Data on 34 patients were presented • Patient characteristics were not reported in detail • No descriptions on interventions • Loss to follow-up was not reported • No sufficient detail on data analysis
Spies 2004, United States[21]	• Prospective study • Interventions and outcomes were described • Funding source was reported	• Sample size determination was not reported in detail; no power calculation • Unclear whether patients in the two treatment groups were enrolled over the same period of time • Imbalanced baseline patient characteristics between groups • No information on loss to follow-up • Unclear whether the participants were representative of the entire population
Razavi 2003, United States[27]	• Interventions and outcomes were described • Patients in the two treatment groups were enrolled over the same period of time • Sample size determination was reported	• Some baseline patient characteristics were not comparable between groups • No information on loss to follow-up • Unclear whether the participants were representative of the entire population • Funding source was not reported
Broder 2002, United States[28]	• Interventions and outcomes were described • Patients in the two treatment groups were enrolled over the same period of time • COI was reported	• Insufficient power to detect significant difference in the primary outcome • Imbalanced baseline patient characteristics between groups • Unclear whether the participants were representative of the entire population • Loss to follow-up was not reported
Sawin 2000, United States[14]	• Interventions and outcomes were described • Sample size calculation was described	• Unclear whether patients in the two treatment groups were enrolled over the same period of time • Imbalanced baseline patient characteristics between groups • Unclear whether the participants were representative of the entire population • Loss to follow-up was not reported • COI was not reported
Iverson 1996, United States[15]	• Interventions and outcomes were described	• Patients in the two treatment groups were enrolled over a wide time range • Imbalanced baseline patient characteristics between groups • Unclear whether the participants were representative of the entire population • COI was not reported

COI = conflict of interest; ITT = intention-to-treat; MRgFU = magnetic resonance-guided focused ultrasound.

Appendix 7: Clinical Evidence — Study Results

Table 7-1: Results — Myomectomy Versus Hysterectomy

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, days
RCTs (no studies)										
Non-RCTs										
Odejinmi 2015[13]										
MYO (n = 216)	NR	NR	NR	NR	NR	-Blood loss (mL): 316.2 ± SD 232.9 -Transfusion: 5 (2.3%)	NR	NR	NR	2.12 ± SD 0.98
HYS (n=184)	NA		NA			-Blood loss (mL): 215.1 ± SD 136.2 -Transfusion: 1 (0.5)				1.81 ± SD 0.64
P for between-group comparisons	NA		NA			-Blood loss: < 0.0001 -Transfusion: NR				= 0.0003
Spies 2010[12]										
MYO (n = 60)	NR	NR	NR	Month 12: SSS in UFS-QOL: 23.4 ± SD 18.9	Month 12: 23.4 ± SD 18.9; HRQL total in UFS-	AEs: 8 patients (13.3%)	NR	3 patients (5%)	NR	1.0

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, days
					QOL: 81.1 ± SD 23.2 Month 12: SF-36 PCS: 52.2 ± SD 8.2 SF-36 MCS: 46.9 ± SD 11.9					
HYS (n = 105)	NA		NA	Month 12: SSS in UFS-QOL: 7.6 ± SD 8.4	Month 12: HRQL total in UFS-QOL: 92.3 ± SD 11.0 Month 12: SF-36 PCS: 52.3 ± SD 8.7 SF-36	AEs: 14 patients (13.3%)	NA	4 patients (3.8%)		1.9 ± 1.3

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, days
					MCS: 50.0 ± SD 10.2					
P for between-group comparisons	NA		NA	NR	HRQL total: < 0.01 SF-36 PCS and MCS: NR	> 0.05	NA	NR		NR
Sawin 2000[14]										
MYO (n = 197)	NR	NR	NR	NR	NR	- Overall morbidity: 38.6%; - Febrile: 33.0% - Hemorrhage: 9.6% - Blood loss: 226.7 ± SD 190.5 - Patient transfused: 18 (9.1%)	NR	NR	NR	3.96 ± SD 2.1
HYS (n = 197)	NA		NA			- Overall morbidity: 40.1%; - Febrile: 25.9% - Hemorrhage: 14.2%;				4.42 ± SD 2.4

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, days
						- Blood loss: 483.6 ± SD 375.8 - Patient transfused: 25 (12.8%)				
P for between-group comparisons	NA		NA			- Overall morbidity: = 0.75 - Febrile: = 0.12 - Hemorrhage: = 0.009 - Blood loss: = 0.00001 - Patient transfused: = 0.25				= 0.048
Iverson 1996[15]										
MYO (n = 103)	NR	NR	NR	NR	NR	- Blood loss (mL): 796 - Transfusion: 29 (28.2%) - Temperature ≥ 38°C after 48 hr: 31 (32%)	NR	NR	NR	NR
HYS (n = 89)	NA		NA			- Blood loss (mL): 464 - Transfusion: 29 (32.6%) - Temperature				

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, days
						≥ 38°C after 48 hr: 44 (49.4%)				
P for between-group comparisons	NA		NA			95% CIs: - Blood loss: 121 to 545 - Transfusion: 0.8 to 1.8 - Temperature ≥ 38°C (relative risk): 1.1 to 2.2				

AE = adverse event; CI = confidence interval; HRQL total = sum of the HRQoL subscales in the UFS-QOL (higher scores indicate better quality of life); HRQoL = health-related quality of life; HYS = hysterectomy; MCS = mental component summary; MYO = myomectomy; NA = not applicable; NR = not reported; PCS = physical component summary; RCT = randomized controlled trial; SD = standard deviation; SF-36 = Short Form (36) Health Survey; SSS = Symptom Severity Scale; UFS-QOL = Uterine Fibroid Symptom and Quality of Life Questionnaire.

Table 7-2: Results (Uterine Artery Embolization Versus Hysterectomy)

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
RCTs										
Ruuskanen 2010[16]										
UAE (n = 27)	Year 2: Substantial improvement in menorrhagia: 12/18 patients (67%)	Year 2: Substantial improvement in pressure symptoms: 19/20 patients (95%)	NR	Year 2: 22 patients (82%) reported substantial symptom relief	NR	Major complications: 0 Minor complications: 1 patient	NR	5 patients	24 patients (89%) would have chosen their performed treatment again	NR
HYS (n = 30)	Year 2: Substantial improvement in menorrhagia: 25/25 patients (100%)	Year 2: Substantial improvement in pressure symptoms: 18/26 patients (69%)	NA	Year 2: 28 patients (93%) reported substantial symptom relief	NR	Major complications: 2 patients Minor complications: NR	NR	3 patients	29 patients (97%) would have chosen their performed treatment again	NR
P for between-group comparisons	= 0.002	= 0.029	NA	= 0.173	NR	Major: = 0.492	NR	NR	= 0.336	NR
Hehenkamp 2005 (EMMY)[17,38-40,65,66,69]										
UAE (n = 88)	2-year: 50/81 showed improvement or free of menorrhagia;	2-year: bulk-related complaints eased in 66.2%;	2-year: uterine volume: ↓48.2%	NR	2-year change from baseline: *SF-36 MCS*: 5.80; *SF-36*	Blood loss: 30.9 mL Pain (24 hr post	NR	2-year: 20/81 patients (24.7%) required re-	2-year: 74/81 (92%) patients were at least moderately	2.0 ± SD 2.1

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
	3 had no change in menorrhagia. 5-year: Of the 58 patients who still had their uterus, 44 (75.9%) were free of menorrhagia or reported great or moderate improvement; 8 (13.8%) reported unchanged menstrual bleeding compared with baseline; 10 patients were menopausal	Moderate to greater improvement in pain: 84.9%	Fibroid size: ↓60.5%		*PCS*: 9.42; *HUI-3*: 0.068; *EQ-5D*: 0.086; *UDI*: –17.03; *IIQ*: –7.14; *DDI*: –14.42; *SAQ*[c] (dimensions of pleasure, discomfort, and habit): 0.89/–0.43/ 0.28. 5-year change from baseline: *SF-36 MCS*: 6.31; *SF-36 PCS*: 8.47; *UDI*: –10.70; *DDI*: –12.72.	intervention): Data were presented graphically Minor[a] complication (from procedure until 6-week visit): 64.2% Major[b] complication (from procedure until 6-week visit): 4.9%		interventions, including 19 secondary HYS, due to bilateral UAE failure or clinical failure during 2-year follow-up 2 to 5 years: 8 patients needed re-interventions, including 4 new secondary HYS In total, 28/81 (34.6%) patients required re-interventions after the primary intervention	satisfied. 5-year: 68/81 (84.0%) patients were at least moderately satisfied.	
HYS (n = 89)	NA	2-year: bulk-related	NA	NR	2-year change from	Blood loss: 436.1 mL	NA	2-year: 5/75 patients	2-year: 66/75 (88%)	5.1 ± SD 1.3

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
		complaints eased in 69.2% Moderate to greater improvement in pain: 78.0%			baseline: *SF-36 MCS*: 7.26; *SF-36 PCS*: 9.32; *HUI-3*: 0.094; *EQ-5D*: 0.102; *UDI*: –14.66; *IIQ*: 1.59; *DDI*: –5.39; *SAQ* (dimensions of pleasure, discomfort, and habit): 1.18/–0.49/ 0.22 5-year change from baseline: *SF-36 MCS*: 6.87; *SF-36 PCS*: 7.20; *UDI*: –8.41; *DDI*: 0.01	Pain (24 hr post intervention): Higher pain scores; data were presented graphically Minor complications: 56.0% Major complications: 2.7%		(6.7%) required re-interventions 2 to 5 years: 3 patients needed re-interventions In total, 8/75 (10.7%) patients required re-interventions after the primary intervention.	patients were at least moderately satisfied. 5-year: 66/75 (88%) patients were at least moderately satisfied.	
P for between-group comparisons	NA	2-year: bulk-related symptoms change: = 0.71	NA	NR	2-year: *SF-36 MCS*: = 0.496; *SF-36 PCS*: = 0.948;	Blood loss: < 0.001 Pain (24 hr post	NA	NR	2-year: = 0.02 5-year: = 0.13	NR

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
		Moderate to greater improvement in pain: = 0.30			*HUI-3*: = 0.462; *EQ-5D*: = 0.620; *UDI*: = 0.656; *IIQ*: = 0.226; *DDI*: = 0.072; *SAQ* (dimensions of pleasure, discomfort, and habit): = 0.74/ 0.88/ 0.74 5-year: *SF-36 MCS*: = 0.806; *SF-36 PCS*: = 0.468; *UDI*: = 0.686; *DDI*: = 0.010	intervention): = 0.012 Minor complications: 0.38 Major complications: 0.68				
Pinto 2002[18e]										
UAE (n = 38)	Month 6: Cessation of bleeding: 31/36 patients (86%)	NR	Month 6: mean dominant UF volume ↓ 46%, from 84.42 cm^3 at baseline to 45.46	NR	NR	Intra-procedural complications: 10/40 patients (25%) ≤ 30 days post-procedure	NR	2/37 patients (5.4%) received HYS due to UAE failure	28/36 patients (78%) indicated they would undergo the same treatment	1.71 ± SD 1.59

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
			cm^3			complications: 29/40 patients (72%)			again; 5 (14%) no; 3 (8%) maybe.	
HYS (n = 19)	NA	NR	NA	NR	NR	Intra-procedural complications: 4/20 patients (20%) ≤ 30 days post-procedure complications: 9/20 patients (45%)	NR	NR	15/17 patients (88%) indicated they would undergo the same treatment again; 2 (12%) no.	5.85 ± SD 2.52
P for between-group comparisons	NA	NR	NA	NR	NR	Intra-procedural complications: = 0.8 ≤ 30 days post-procedure complications: = 0.05	NR	NA	NR	< 0.001
Non-RCTs										
Spies 2010[12]										
UAE (n = 105)	NR	NR	NR	Month 12: SSS in UFS-QOL: 24.9 ± SD 18.6	Month 12: HRQL total in UFS-QOL: 82.9 ± SD 20.0	AEs[d]: 7 patients (6.7%)	NR	0	NR	1.0 ± SD 0.0

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
					Month 12: SF-36 PCS: 51.6 ± SD 6.7 SF-36 MCS: 50.8 ± SD 8.9					
HYS (n = 105)	NA	NR	NA	Month 12: SSS in UFS-QOL: 7.6 ± SD 8.4	Month 12: HRQL total in UFS-QOL: 92.3 ± SD 11.0 Month 12: SF-36 PCS: 52.3 ± SD 8.7 SF-36 MCS: 50.0 ± SD 10.2	AEs: 14 patients (13.3%)	NA	4 patients (3.8%)	NR	1.9 ± SD 1.3
P for between-group comparisons	NA	NR	NA	NR	HRQL total: < 0.01 SF-36 PCS and MCS: NR	> 0.05	NA	NR	NR	NR
Brochner 2009[19]										
UAE (n = 20)	NR	NR	NR	NR	NR	NR	NR	3 patients (15%)	17 patients (85%)	< 24 hours
HYS (n = 20)	NA	NR	NA	NR	NR	NR	NA	NR	NR	Median 4 days (range 3 to 5)

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
P for between-group comparisons	NA	NR	NA	NR	NR	NR	NA	NR	NR	NR
Dutton 2007 (HOPEFUL)[20,46]										
UAE (n = 649)	NR	NR	NR	Symptoms relieved: 472 patients (85.2%)	NR	Total complications: 114 patients (17.6%) Severe complications: 1 patient 0.2%) Major complications: 24 patients (3.7%) Minor complications: 89 patients (13.7%) No complications: 535 (82.4%)	In 303 women who indicated that they wished for or were uncertain about their wish for children, 27 women (8.5%) had 37 pregnancies: 19 live births (79% C-section), 15 miscarriages, 2 ectopic pregnancies, and 1 termination	119 patients (18.3%) needed further treatments for UF	Recommend to friend: 510 patients (91.4%) Expectation fulfilled: 417 patients (73.5%)	NR
HYS (n = 459)	NA	NR	NA	Symptoms relieved: 352 patients (99.2%)	NR	Total complications: 120 patients (26.1%)	NA	NA	Recommend to friend: 278 patients (85.5%)	NR

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
						Severe complications: 3 patients (0.7%) Major complications: 49 patients (10.7%) Minor complications: 68 patients (14.8%) No complications: 339 patients (73.9%)			Expectation fulfilled: 343 patients (93.5%)	
P for between-group comparisons	NA	NR	NA	< 0.0001	NR	Total complications: = 0.001 Severe or major complications: < 0.0001	n/a	n/a	Recommend to friend: = 0.007 Expectation fulfilled: < 0.0001	NR
Spies 2004[21]										
UAE (n = 102)	*Self-assessed*	Month 6: % of patients	Month 3: ↓45.8%	NR	*SF-12 Physical*	% of patients with ≥ 1 AE:	NR	NR	% of moderately	0.83

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
	blood loss score: Month 3:↓55.6% (435.6 ± SD 286.5 at baseline to 161.1 ± SD 133.3); Month 6:↓58.1% (to 140.6 ± SD 110.1) *Menorrhagia questionnaire*: Month 3: ↓46.8% (47.2 ± SD 13.8 at baseline to 23.3 ± SD 11.2); month 6: ↓56.6% (to 19.2 ± SD 8.3); year 1: ↓61.3% (to 17.3 ± SD 10.2).	with improved pelvic pain: 83%; % of patients with improved pelvic discomfort: 80%; improved urinary dysfunction: 75% Year 1: % of patients with improved pelvic pain: 84%; % of patients with improved pelvic discomfort: 83%; improved urinary dysfunction: 80%	Month 6: ↓54.0%		*summary*: Month 3: ↑19.5% (45.1 ± SD 8.2 at baseline to 52.3 ± SD 6.0); Month 6: ↑22.3% (to 53.4 ± SD 5.0); Year 1: ↑22.6% (to 53.6 ± SD 6.1) *SF-12 Mental summary*: Month 3: ↑21.4% (45.4 ± SD 11.5 at baseline to 52.0 ± SD 7.5); month 6: ↑24.5% (to 53.1 ± SD 7.6); year 1: ↑23.4% (to 52.6 ± SD 7.9)	28 (27.5%) Complications ≤ 30 days of procedure: 17.6% Complications > 30 days of procedure: 12.7% Minor[f] complications: 29 patients (28.4%) Major[g] complications: 4 patients (3.9%)			or very satisfied at Month 3: 89%; month 6: 88%; year 1: 90%	

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
					Overall health status at month 3: from 71.1 at baseline ↑to 83.6					
HYS (n = 50)	NA	Month 6: % of patients with improved pelvic pain: 88%; % of patients with improved pelvic discomfort: 80%; improved urinary dysfunction: 73% Year 1: % of patients with improved pelvic pain: 98%; % of patients with improved pelvic discomfort: 95%; improved urinary dysfunction:	NA		*SF-12 Physical summary*: Month 3: ↑22.3% (43.0 ± SD 9.9 at baseline to 50.7 ± SD 6.6); month 6: ↑26.0% (to 51.6 ± SD 7.5); year 1: ↑25.4% (to 51.4 ± SD 6.9) *SF-12 Mental summary*: Month 3: ↑38.4% (40.6 ± SD 11.1 at baseline to 51.7 ± SD 10.5); month 6:	% of patients with ≥ 1 AE: 25 (50%) Complications ≤ 30 days of procedure: 28% Complications > 30 days of procedure: 32% Minor complications: 26 patients (52%) Major complications: 6 patients (12%)	NA	NR	% of moderately or very satisfied at month 3: 94%; month 6: 94%; year 1: 97%	2.3

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
		79%			↑32.3% (to 49.7 ± SD 11.8); year 1: ↑39.1% (to 51.1 ± SD 11.2). Overall health status at month 3: from 67.5 at baseline ↑to 86.1					
P for between-group comparisons	NA	Month 6: pelvic pain: = 0.478; pelvic discomfort: = 1.0; urinary dysfunction: = 0.841 Year 1: pelvic pain: = 0.021; pelvic discomfort: = 0.055; urinary	NA		Overall health status at month 3: = 0.26	% of patients with ≥ 1 AE: = 0.01 Early complications: = 0.15 Late complications: =0.01 Major complications: =0.08	NA	NR	All > 0.05	< 0.001

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/ re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
		dysfunction: = 0.819								

AE = adverse event; C-section = Caesarean section; DDI = Defecation Distress Inventory (higher score indicates worse outcome); EQ-5D = EuroQol 5-Dimension Questionnaire; HRQL total = the HRQoL subscales in the UFS-QOL (higher scores indicate better quality of life); HRQoL = health-related quality of life; HUI-3 = the Health Utilities Index Mark 3 (higher score indicates favourable outcome); HYS = hysterectomy; IIQ = Incontinence Impact Questionnaire (higher score indicates worse outcome); MCS = mental component summary (higher score indicates more favourable outcome); NA = not applicable; NR = not reported; PCS = physical component summary (higher score indicates more favourable outcome); RCT = randomized controlled trial; SAQ = the Sexual Activity Questionnaire (for dimensions of pleasure and habit, higher scores indicate more favourable outcome, while for dimension of discomfort, higher score indicates worse outcome); SD = standard deviation; SF-36: Short Form (36) Health Survey; SSS = Symptom Severity Scale (of UFS-QOL); UAE = uterine artery embolization; UDI = Urogenital Distress Inventory (higher score indicates worse outcome); UF = uterine fibroid; UFS-QOL = the Uterine Fibroid Symptom and Quality of Life questionnaire (higher scores in Symptom Severity subscale indicate greater symptom severity; higher quality of life scores indicate better quality of life).

[a] "Minor complication" was listed for all non-major complications.

[b] "Major complication" was defined as meaning the events were potentially life-threatening, could lead to permanent sequelae, or required surgical intervention.

[c] SAQ was filled out only by patients who were sexually active during the month before receiving the questionnaire. At 24 months, 52% of patients in the UAE and 31% of patients in HYS groups were sexually active ($P = 0.118$).

[d] "Adverse event" was not defined in the Spies study. This outcome included the following: requirement of unanticipated medical therapy, delay of normal hospital discharge by > 24 h, need for emergency department evaluation or care, readmission to hospital, need for increased level of care (intensive care unit), need for additional surgery or invasive procedures, permanent injury, or death.

[e] All outcomes were measured in per-treatment population, except for "length of hospital stay," where an intention-to-treat analysis was performed.

[f] "Minor complication" was defined as no therapy, no consequences, requiring nominal therapy, observation but no consequences.

[g] "Major complication" was defined as requiring therapy, minor hospitalization (< 48 hours), major therapy, unplanned increase level of care, prolonged hospitalization (≥ 48 hours), permanent adverse sequelae, or death.

Table 7-3: Results (Uterine Artery Embolization Versus Myomectomy)

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
RCTs										
Manyonda 2012[22]										
UAE (n = 74)	NR	NR	NR	Year 1: SSS: ↓ 30.4 ± SD 25.3 from baseline	Year 1: Total HRQL: ↑ 32.3 ± SD 28.8 from baseline	Minor: 9 patients (13.2%) Major: 2 patients (2.9%)	NR	9 patients (14.8%)	NR	2.0
MYO (n = 73)				Year 1: SSS: ↓ 37.6 ± SD 27.2 from baseline	Year 1: Total HRQL: ↑ 39.9 ± SD 27.3 from baseline	Minor: 8 patients (10.9%) Major: 6 patients (8%)		3 patients (4%)		6.0
P for between-group comparisons				= 0.13	= 0.14	Minor: = 0.4 Major: = 0.28		= 0.067		< 0.0001
Mara 2008[23]										
UAE (n = 58)	NR	NR	Mean ↓ of diameter of dominant UF by ultra-sound: 31.7%	Symptom relief at month 6: 46/52 (88.5%)	NR	Peri-procedural complications: 4 patients (6.9%) Early post-procedural complications: 12 patients	26 patients tried to conceive: 13 (50%) became pregnant; 5 (19.2%) had delivered.	19 patients (32.8%); mean interval from initial UAE to re-intervention was 12.4 months	NR	60.2 ± SD 32.3 hours

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
						(20.7%) Late post-procedural complications: 8 patients (13.8%) Transfusions: 0	5 deliveries: 0 preterm delivery, 3 C-sections, 1 postpartum hemorrhage, 0 fetal intrauterine growth restrictions			
MYO (n = 63)			NA	Symptom relief at month 6: 51/58 (87.9%)		Peri-procedural complications: 5 patients (7.9%) Early post-procedural complications: 10 patients (15.9%) Late post-procedural complications: 8 patients (13.8%) Transfusions: 2 (3.2%)	40 patients tried to conceive: 31 (77.5%) became pregnant, 19 (47.5%) had delivered. 19 deliveries: 5 preterm delivery, 13 C-sections, 0 postpartum hemorrhage, 2 fetal intrauterine growth restrictions	2 patients (3.2%), 15- and 30-month after initial MYO, respectively.		86.1 ± SD 40.4

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
P for between-group comparisons			NA	Symptom relief at month 6: > 0.05		> 0.05 for peri, early post-, or late post-procedural complications and transfusions	Became pregnant: > 0.05 Delivery: < 0.05 > 0.05 for all perinatal outcomes	< 0.0001		< 0.0001
Non-RCTs										
Spies 2010[12]										
UAE (n = 105)	NR	NR	NR	NR	Month 12: - SSS in UFS-QOL: 24.9 ± SD 18.6; - HRQL total in UFS-QOL: 82.9 ± SD 20.0 Month 12: - SF-36 PCS: 51.6 ± SD 6.7 - SF-36 MCS: 50.8 ± SD 8.9	AEs: 7 patients (6.7%)	NR	0	NR	1.0 ± 0.0
MYO (n = 60)					Month 12: - SSS in UFS-QOL: 23.4 ± SD 18.9; - HRQL total in UFS-QOL: 81.1 ± SD 23.2	AEs: 8 patients (13.3%)		3 patients (5%)		2.1 ± 1.0

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
					Month 12: - SF-36 PCS: 52.2 ± SD 8.2 - SF-36 MCS: 46.9 ± SD 11.9					
P for between-group comparisons					> 0.05 for all comparisons	> 0.05		NR		NR
Narayan 2010[24]										
UAE (n = 87)	NR	NR	NR	SSS: ↓ from 53.6 pre-procedure to 15.0 post-procedure	NR	Transfusion: adjusted OR, UAE vs. MYO: 0.049 (95% CI, 0.006 to 0.42)	NR	Adjusted OR, UAE vs. MYO: 0.97 (95% CI, 0.27 to 3.52)	Adjusted OR, UAE vs. MYO: 1.36 (95% CI, 0.47 to 3.96)	Adjusted OR, UAE vs. MYO: 0.0036 (95% CI, 0.0003 to 0.0377)
MYO (n = 98)				SSS: ↓ from 48.6 pre-procedure to 22.6 post-procedure						
P for between-group comparisons				NR		Transfusion: = 0.006		NR	= 0.57	= 0.000

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
Goodwin 2006[25]										
UAE (n = 149)	Change in mean menstrual bleeding scores from baseline: month 3: –24.5 (–49.2%); month 6: –26.6 (–55.2%); year 1: –28.6 (–61.1%)	NR	Change from baseline: month 3: –37.7%; month 6: –53.9%	NR	Month 6: 141 patients (94.6%) achieved a ≥ 5-point increase in UFQoL score Overall HRQoL: Significantly improved at month 6 from baseline in all domains	% of patients with AEs: 33 (22.1%) Number of AEs: 53 in total, 24 (45.3%) were procedure-related. Major events[a]: 6, 3 were procedure-related.	Year 1: no pregnancy was reported.	3 (2.0%) Year 1: 2/120 required additional pharmaceutical therapy.	NR	23.8 hours, SD NR
MYO (n = 60)	Change in mean menstrual bleeding scores from baseline: month 3: –22.8 (– 43.0%); month 6: –24.1 (– 46.1%)		NA		Month 6: 55 patients (91.7%) achieved a ≥ 5-point increase in UFQoL score Overall HRQoL: Significantly improved at month 6 from baseline in all domains	% of patients with AEs: 24 (40%) Number of AEs: 43 in total; 22 (51.2%) were procedure-related Major events: 1, procedure-related.	NR	1 (1.7%) converted to HYS at time of MYO		61.6 hours, SD NR

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
P for between-group comparisons	> 0.05 for both month 3 and month 6		NA		Overall HRQoL: > 0.05 for all comparison at month 6	% of patients with AEs: = 0.01 Major events: > 0.05	NR	NR		< 0.0001
Siskin 2006[26]										
UAE (n = 77)	Change in mean menorrhagia bleeding scores from baseline: month 3: –46.0%; month 6: –52.1%; year 1: –58.2%; year 2: –61.0%	NR	Change from baseline: Month 3: -38.5% month 6: -43.7%	NR	*UFQoL*: - Month 6: 68 patients (88.3%) achieved a ≥ 5-point increase in UFQoL score - Year 1 and year 2: Significant change from baseline scores in all measures, except for hot flashes *Overall HRQoL*: Significantly improved from baseline in all domains	% of patients with AEs: 20 patients (26.0%) Number of AEs: 26 in total; 12 (46.2%) were procedure-related — all minor[b]	Year 1: No pregnancies Year 2: 2 unplanned pregnancies (1 spontaneous abortion; 1 elective termination)	Year 1: 3/71 patients required additional treatment (1 drug therapy; 2 HYS)	NR	22.0 hours (range 2 to 47)

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
MYO (n = 69)	Change in mean menorrhagia bleeding scores from baseline: month 3: –40.0%; month 6: –43.7%		NA		*UFQoL*: month 6: 52 (75.4%) achieved a ≥ 5-point increase in UFQoL score *Overall HRQoL*: Significantly improved from baseline in all domains	% of patients with AEs: 29 patients (42.0%) Number of AEs: 53 in total; 30 (56.6%) were procedure-related — 28 were minor and 2 were major[a]	NR	1 (1.4%) patients converted to HYS during the baseline MYO		60.2 hours (range 7 to 196)
P for between-group comparisons	NR		NA		≥ 5-point increase in UFQoL: = 0.041 No significant differences found in the overall HRQoL measures between groups. *P* value NR	% of patients with AEs: = 0.041				NR

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
Razavi 2003[27]										
UAE (n = 67)	Completely resolved or significantly improved: 48/52 patients (92%)	Completely resolved or significantly improved: 28/37 patients (76%)	NR	NR	NR	AEs: 7 patients (11%)	NR	5/62 patients (8%)	NR	0
MYO (n = 44)	Completely resolved or significantly improved: 14/22 patients (64%)	Completely resolved or significantly improved: 21/23 patients (91%)	NA			AEs: 10 patients (25%)		4/40 patients (10%)		2.9 (range 2 to 7)
P for between-group comparisons	< 0.05	< 0.05	NA			< 0.05		> 0.05		< 0.05
Broder 2002[28]										
UAE (n = 51)	NR	NR	NR	Median score improved: 6 points (range –3 to 15)	NR	NR	NR	15 (29%)	34/36 (94%) at least somewhat satisfied	NR
MYO (n = 30)				Median score improved:				1 (3%)	23/29 (79%) somewhat or	

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
				5 points (range –1 to 23)					very dissatisfied	
P for between-group comparisons				= 0.44				= 0.004	= 0.06	

AE = adverse event; C-section = Caesarean section; CI = confidence interval; HRQL = the HRQoL subscales in the UFS-QOL (higher scores indicate better quality of life); HRQoL = health-related quality of life; HYS = hysterectomy; MCS = mental component summary (of Short Form [36] Health Survey); MYO = myomectomy; NA = not applicable; NR = not reported; OR = odds ratio; PCS = physical component summary (of Short Form [36] Health Survey); RCT = randomized controlled trial; SD = standard deviation; SSS = Symptom Severity Scale (of UFS-QOL); UAE = uterine artery embolization; UF = uterine fibroid; UFQoL = Uterine Fibroid Quality of Life Questionnaire; UFS-QOL = the Uterine Fibroid Symptom and Quality of Life questionnaire (consists of Symptom Severity scale and the HRQL subscales (higher scores in the former indicate greater symptom severity, while higher scores in the latter indicate better quality of life); vs. = versus.

[a] "Major event" was defined as requiring major therapy or increase in care beyond 48 hours, permanent adverse sequelae, or death.

[b] "Minor event" was defined as not requiring therapy or result in any consequences, requiring nominal therapy including observational overnight admission, or requiring treatment and/or hospitalization for ≤ 48 hours without sequelae.

Table 7-4: Results (Uterine Artery Embolization Versus Uterine Artery Occlusion)

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
RCTs										
Helal 2010[29]										
UAE (n = 45)	Year 1: bleeding reduction in 40 patients (88.9%) Year 1 mean reduction in bleeding: 91.9%	Year 1: pressure reduction in 36 patients (80%)	NR	NR	NR	NR	NR	NR	NR	NR
UAO (n = 45)	Year 1: bleeding reduction in 39 patients (86.7%) Year 1 mean reduction in bleeding: 93.3%	Year 1: pressure reduction in 35 patients (80%)								
P for between-group comparisons	Number of patients reporting bleeding	= 0.88								

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
	reduction: = 0.69									
Ambat 2009[30]										
UAE (n = 10)	NR	NR	Month 3: UF volume ↓15.8% Month 6: UF volume ↓43%	Month 3: mean PBAC score ↓47.3% Month 6: mean PBAC score ↓59.6%	NR	Post-operative pain score: 6.5	NR	NR	NR	3.5 (range 2 to 7)
UAO (n = 10)			Month 3: UF volume ↓34.3% Month 6: UF volume ↓33.6%	Month 3: mean PBAC score ↓69.2% Month 6: mean PBAC score ↓41%		Post-operative pain score: 2.75				3.5 (range 2 to 10)
P for between-group			Month 3: = 0.075	Month 3: = 0.165		= 0.0002				= 1.0

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
comparisons			Month 6: = 1.0	Month 6: = 0.436						
Cunningham 2008[31]										
UAE (n = 8)	NR	NR	NR	Month 3: mean AMSS score ↓58%	NR	Post-procedural pain score: 5 ± SD 3.2	NR	NR	NR	6 ± SD 0.7
UAO (n = 6)				Month 3: mean AMSS score ↓63%		Post-procedural pain score: 1 ± SD 1.5				1 ± SD 0.4
P for between-group comparisons				NR		= 0.03				= 0.09
Hald 2007[32]										
UAE (n = 29)	Month 6: bleeding reduction in 26 patients (89.7%)	Month 6: reduction in 20 patients (69.0%)	Month-6: % reduction in dominant UF volume: 62.8 ± SD 27.0 (based on 26 patients)	Symptom-free at month 6: 20 (69.0%) Month 3: mean PBAC score ↓45%	NR	Pain after UAE measured by VAS: 2.41 ± SEM 0.27 cm AEs during hospitalization: 4 patients (13.8%)	NR	7 patients (24.1%)	Partly or totally satisfied: 27 (93.1%)	Average 57 hours (range 24 to 108)

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
				Month 6: mean PBAC score ↓52%		AEs from discharge to month 6: 15 patients (51.7%)				
UAO (n = 29)	Month 6: bleeding reduction in 25 patients (86.2%)	Month 6: reduction in 17 patients (58.6%)	Month 6: % reduction in dominant UF volume: 55 ± SD 22.1 (based on 22 patients)	Symptom-free at month 6: 15 (51.7%) Month 3: mean PBAC score ↓47% Month 6: mean PBAC score ↓53%		Pain after UAE measured by VAS: 1.00 ± SEM 0.27 cm AEs during hospitalization: 3 patients (10.3%) AEs from discharge to month 6: 9 patients (31.0%)		6 patients (20.7%)	Partly or totally satisfied: 24 (93.1%)	Average 46 hours (range 24 to 72)
P for between-group comparisons	= 0.69	= 0.88	= 0.083	Symptom-free: = 0.18		Pain: = 0.026		NR	= 0.23	= 0.001

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
Non-RCTs										
Mara 2012, Czech Republic[33]										
UAE (n = 100)	NR	NR	Based on 90 patients, month 6: ↓ in diameter of dominant UF: 28.5% ↓ in volume of dominant UF: 53.0%	Patients with persistent symptoms at month 6: 7 (7%) Patients with symptom recurrence after month 6: 3 (3%)	NR	Overall complications: 28 events Peri-procedural complications: 1 event Early post-procedural complications: 19 events Late post-procedural complications: 8 events	Number of pregnant women: 29/42 (69.0%) Number of deliveries: 23/42 (54.8%) Number of cases of post-procedural sterility: 13/42 (31.0%) Mean gestation week in women who delivered: 38.1 ± SD 1.6 Preterm delivery: 1/23 (4.3%)	39 patients (39%) Re-intervention due to failure, recurrence or complication: 12 patients (12%)	NR	2.4 ± SD 1.1

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
							C-section rate: 78.3%			
UAO (n = 100)			Based on 92 patients, month 6: ↓ in diameter of dominant UF: 22.3% ↓ in volume of dominant UF: 39.0%	Patients with persistent symptoms at month 6: 8 (8%) Patients with symptom recurrence after month 6: 3 (3%)		Overall complications: 11 events Peri-procedural complications: 1 event Early post-procedural complications: 8 events Late post-procedural complications: 2 events	Number of pregnant women: 32/48 (66.7%) Number of deliveries: 22/48 (45.8%) Number of cases of post-procedural sterility: 16/48 (33.3%) Mean gestation week in women who delivered: 38.0 ± SD 3.5 Preterm delivery: 2/22 (9.1%)	15 patients (15%) Re-intervention due to failure, recurrence or complication: 10 patients (10%)		2.3 ± 0.8

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
							C-section rate: 78.3%			
P for between-group comparisons			↓ in diameter and volume of UF: > 0.05	> 0.05		Overall: = 0.002 Peri-procedural: > 0.05 Early: = 0.023 Late: = 0.048	All > 0.05	Number of patients required re-intervention: = 0.001		> 0.05
Holub 2006[34]										
UAE (n = 14 conceived)	NR	NR	NR	NR	NR	NR	Number of pregnancies: 17 Abortions: 7/16 (43.7%) Preterm deliveries: 1 (12.5%) C-sections: 6 (75%) Mean gestational age: 38.3 weeks	NR	NR	NR
UAO (n = 20 conceived)							Number of pregnancy: 22			

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
							Abortions: 3/20 (15%) Preterm deliveries: 2 (14.2%) C-sections: 8 (57.2%) Mean gestational age: 38.8 weeks			
P for between-group comparisons							Abortions: < 0.05. All others: > 0.05			

AE = adverse event; AMSS = Aberdeen Menorrhagia Severity Scale; C-section = Caesarean section; HRQoL = health-related quality of life; NA = not applicable; NR = not reported; PBAC = Pictorial Bleeding Assessment Chart; RCT = randomized controlled trial; SD = standard deviation; SEM = standard error of the mean; UAE = uterine artery embolization; UAO = uterine artery occlusion; UF = uterine fibroid; VAS = visual analogue scale.

Table 7-5: Results (Uterine Artery Embolization Versus MRgFU)

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day (mean ± SD)
RCTs (no studies)										
Non-RCTs										
Ikink 2014[35]										
UAE (n = 68)	NR	NR	Month 3: ↓ in UF volume: 43.3% (IQR 29.9 to 65.0)	Month 3: tSSS ↓ from 65.3 at baseline to 21.9 (IQR 9.4 to 34.4)	Month 3: total HRQoL score in UFS-QOL: ↑from 48.5 at baseline to 85.4 (IQR 75.2 to 94.6)	13 events	NR	Year 1: 3 patients (4.5%) Median follow-up of 24 months: 5 patients (7%)	NR	NR
MRgFU (n = 51)			Month 3: ↓ in UF volume: 17.2% (IQR 3.2 to 34.5)	Month 3: tSSS ↓ from 53.1 at baseline to 34.4 (IQR 21.9 to 46.9)	Month 3: total HRQoL score in UFS-QOL: ↑from 60.3 at baseline to 81.5 (IQR 57.6 to 90.3)	No complications or AEs reported		Year 1: 18 patients (35%) Median follow-up of 15 months: 24 patients (47%)		
P for between-group comparisons			< 0.001	< 0.001	< 0.001	NR		Year 1: = 0.002		

AE = adverse event; HRQoL = health-related quality of life; IQR = interquartile range; MRgFU = magnetic resonance-guided focused ultrasound; NA = not applicable; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; tSSS = transformed Symptom Severity Score; UAE = uterine artery embolization; UF = uterine fibroid; UFS-QOL = the Uterine Fibroid Symptom and health-related Quality of Life Questionnaire.

Table 7-6: Results (MRgFU Versus Hysterectomy)

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day (mean ± SD)
RCTs (no studies)										
Non-RCTs										
Taran 2009[36,42]										
MRgFU (n = 109)	NR	NR	NR	Month 6: tSSS ↓ from 61.7 at baseline to 37.7 ± SD 21.2.	SF-36: PF: 82.5 ± SD 15.9 PR: 68.3 ± SD 31.0 BP: 69.1 ± SD 19.2 GH: 69.3 ± SD 15.1 VI: 59.1 ± SD 15.1 SF: 79.5 ± SD 18.4 ER: 75.0 ± SD 30.1 MH: 73.3 ± SD 11.7	Fever[a]: 3 (2.8%) Transfusion: 3 (2.8%) Unintended surgical procedures related to treatment[b]: 0 ≥ 1 AE: 88 (81%) SAE: 9 (8%)	NR	Month 6: 4 patients (3.7%): 3 HYS and 1 UAE	NR	NR
HYS (n = 83)				NA	SF-36: PF: 86.9 ± SD 19.2 PR: 80.0 ± SD 37.6 BP: 79.5 ± SD 22.6 GH:	Fever: 12 (14.5%) Transfusion: 6 (7.2%) Unintended surgical procedures		NA		

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL (mean ± SD)	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day (mean ± SD)
					75.3 ± SD 18.4 VI: 65.6 ± SD 20.1 SF: 84.8 ± SD 22.6 ER: 78.1 ± SD 36.8 MH: 79.6 ± SD 15.1	related to treatment: 4 (4.8%) ≥ 1 AE: 82 (99%) SAE: 8 (10%)				
P for between-group comparisons				NA	SF-36: PF: > 0.05 PR: = 0.05 BP: = 0.004 GH: = 0.04 VI: = 0.04 SF: > 0.05 ER: > 0.05 MH: = 0.008	Transfusion: = 0.005 Transfusion: > 0.05 Unintended surgical procedures related to treatment: > 0.05 ≥ 1 AE: < 0.0001 SAE: > 0.05		NA		

AE = adverse event; HRQoL = health-related quality of life; HYS = hysterectomy; MRgFU = magnetic resonance-guided focused ultrasound; NA = not applicable; NR = not reported; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation; SF-36 = Short Form (36) Health Survey (subscales: PF = physical functioning; PR = physical role; BP = bodily pain; GH = general health; VI = vitality; SF = social functioning; ER = emotional role; MH = mental health); tSSS = transformed Symptom Severity Score; UAE = uterine artery embolization.

[a] > 38°C on any 2 post-treatment days

[b] "Unintended surgical procedures related to treatment" included removal of foreign body from the bladder, surgical repair of hernia, revision of enterotomy, and surgical repair of an iatrogenic colonic lesion.

Table 7-7: Results (Myomectomy Versus Radiofrequency Volumetric Thermal Ablation)

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
RCTs										
Brucker 2014,[37] Hahn 2015[11]										
MYO (n = 25)	Year 1: heavy uterine bleeding: 2/22 patients (9.1%) MIQ at year 1: 84.3% reported "better" or "about the same" for the perception of blood loss from the previous period	Year 1: pelvic discomfort: 2/22 patients (9.1%)	Number of treated UFs: 2.0 ± SD 1.4	Year 1 SSS score in UFS-QOL: ↓ 17.9 to 23.4	Year 1 EQ-5D: ↑8.9 from 72.3 at baseline HRQL total score in UFS-QOL ↑ 13.1 to 83.2	Blood loss (mL): 51 ± SD 57 1 suprapubic port site hematoma; no other complications	3 pregnancies; 2 full-term deliveries	No re-intervention	Year 1: 86.5% reported "very satisfied"; 13.6% reported "moderately satisfied"	29.9 ± SD 14.2 hours
RFVTA (n = 25)	Year 1: heavy uterine bleeding: 7/21 patients (33.3%) MIQ at year 1: 94.4% reported "better" or "about the	Year 1: pelvic discomfort: 1/21 patients (4.8%)	Number of treated UFs: 2.8 ± SD 2.6	Year 1 SSS score in UFS-QOL: ↓ 7.8 to 26.2	Year 1 EQ-5D: ↑2.0 from 81.7 at baseline. HRQL total score in UFS-QOL: ↑ 7.5 to 86.4.	Blood loss (mL): 16 ± SD 9 1 unplanned hospitalization due to vertigo; no other complications	2 pregnancies, 2 full-term deliveries	3 re-interventions	Year 1: 42.9% reported "very satisfied"; 42.9% reported "moderately satisfied"	10.0 ± SD 5.5 hours

Studies	Change in abnormal uterine bleeding	Change in pelvic pressure	Change in fibroid size	Symptom scores	HRQoL	Complications (operational, pregnancy)	Pregnancy outcomes (infertility, miscarriage, bleeding during pregnancy, full-term delivery)	Relapse/re-intervention	Patient satisfaction, n (%)	Length of hospital stay, day
	same" for the perception of blood loss from the previous period									
P for between-group comparisons	Heavy uterine bleeding: = 0.088 MIQ: = 0.12	= 1.00	= 0.30	= 0.16	EQ-5D: = 0.24 HRQL total score: = 0.46	Blood loss: < 0.001	NR	NR	= 0.004	< 0.001
Non-RCTs (no studies)										

EQ-5D = EuroQol 5-Dimensions questionnaire; HRQL total = sum of the health-related quality of life subscales in the UFS-QOL (higher scores indicate better quality of life); HRQoL = health-related quality of life; MIQ = Menstrual Impact Questionnaire; MYO = myomectomy; NA = not applicable; NR = not reported; RCT = randomized controlled trial; RFVTA = radiofrequency volumetric thermal ablation; SD = standard deviation; SSS = Symptom Severity Scale (of UFS-QOL); UF = uterine fibroid; UFS-QOL = the Uterine Fibroid Symptom and Quality of Life questionnaire (consists of Symptom Severity Scale and health-related quality of life questions. Higher scores in the former indicate greater symptom severity, while higher scores in the latter indicate better quality of life).

Appendix 8: Economic Evidence — Study Characteristics

Table 8-1: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Analysis, Perspective	Intervention and Comparator(s)	Study Population	Time Horizon	Main Assumptions
Babashov 2015, Canada[43] No competing interests declared. Produced for Health Quality Ontario	Cost-utility analysis Ontario public-payer perspective	MRgFU, UAE, myomectomy, hysterectomy	Premenopausal women, aged 40 to 51 years, with symptomatic uterine fibroids, for whom pharmacotherapy had been ineffective	11 years (until menopause, at age 51)	• Women reach menopause at age 51 • All patients eligible for hysterectomy and myomectomy; 90% eligible for UAE • 35% (base case) or 100% (alternative scenario) of patients eligible for MRgFU • Patients with symptom recurrence would be re-treated with the same intervention upon first recurrence (maximum 3 rounds of treatment) • Patients with first-line treatment failure would receive second-line treatment with the next least invasive procedure (maximum 3 rounds of treatment) • Third-line treatment was always hysterectomy • Utility decrements applied for complications • 5% discount rate
Cain-Nielsen 2014, United States[44] Funded by NIH grant; one author disclosed research and consulting funds from	Cost-utility analysis Societal perspective	MRgFU, UAE, myomectomy	Premenopausal women with symptomatic uterine fibroids who wish to retain their uteri	5 years	• 35% of patients eligible for MRgFU, 90% eligible for UAE, 100% eligible for myomectomy • Patients would undergo myomectomy if they failed either MRgFU or UAE or had fibroid recurrence • Costs of major complications were assumed to be

First Author, Publication Year, Country	Type of Analysis, Perspective	Intervention and Comparator(s)	Study Population	Time Horizon	Main Assumptions
industry					captured by the top 25% of costliest patients • QoL scores for UAE were used to approximate those of myomectomy • Patients who experienced a major complication would have a 20% reduction in QoL at time of treatment • Sensitivity analysis: 75% 5-year recurrence rate • 3% discount rate
Kong 2014, United States[45] NIH and industry funding	Cost-utility analysis Societal perspective	MRgFU, UAE, hysterectomy	Premenopausal women (age 40) with symptomatic uterine fibroids	11 years (until menopause, at age 51)	• Women reach menopause at age 51 • 35% of patients eligible for MRgFU, 90% eligible for UAE, 100% eligible for hysterectomy • Patients with no symptom relief would be re-treated with the next least invasive strategy • Patients with symptom recurrence would be re-treated with the same first-line intervention • Patients are treated either until their symptoms resolve or until menopause at age ≥ 51 • Fibroids are assumed to resolve after age 51 • No major or minor complications for MRgFU • Lost productivity costs for hysterectomy complications

First Author, Publication Year, Country	Type of Analysis, Perspective	Intervention and Comparator(s)	Study Population	Time Horizon	Main Assumptions
					included within the lost-productivity costs of the procedure • 3% discount rate
O'Sullivan 2009, United States[4] Industry funding	Cost-utility analysis Societal perspective	MRgFU, UAE, myomectomy, hysterectomy, pain management with pharmacotherapy	Premenopausal women (mean age 40 years) with symptomatic uterine fibroids	Lifetime horizon	• All women are eligible for treatment with hysterectomy, myomectomy, or pharmacotherapy, 90% eligible for UAE, 35% eligible for MRgFU • Patients ineligible for MRgFU or UAE assumed to prefer least invasive of remaining treatment options (except pharmacotherapy) • Patients are treated until symptoms have resolved; constant risk of symptom recurrence until menopause • Patients with symptom recurrence would be re-treated with the same intervention • Patients with first-line treatment failure receive second-line treatment with an alternative, more invasive procedure • Third-line treatment is always hysterectomy • Reference case analysis: loss of productivity costs assumed to be reflected in the utility estimates (omitted from cost estimates) • Major complication rates equal for myomectomy and

First Author, Publication Year, Country	Type of Analysis, Perspective	Intervention and Comparator(s)	Study Population	Time Horizon	Main Assumptions
					hysterectomy • No further treatment modelled for pharmacotherapy if treatment failed • 3% discount rate
Hirst 2008 (HOPEFUL), United Kingdom[46] Funded by the UK Department of Health	Cost-utility analysis United Kingdom public-payer perspective	UAE, hysterectomy	Premenopausal women (aged 44 to 55 years) with symptomatic uterine fibroids	11 years (until menopause, at age 55)	• Women undergo menopause at age 55 • Patients with UAE failure would have additional procedures (UAE, myomectomy, or hysterectomy) • Myomectomy assumed to have the same cost and utilities as hysterectomy • Utility decrements applied for complications • 3.5% discount rate
Zowall 2008, United Kingdom[47] Industry funding	Cost-utility analysis United Kingdom public-payer perspective	MRgFU, current treatment (25% UAE, 25% myomectomy, 50% hysterectomy)	Women (aged 39 to 56 years) for whom surgical treatment for symptomatic uterine fibroids is being considered	17 years (until menopause, at age 56)	• Initial in-hospital cost of UAE, hysterectomy and myomectomy assumed to be the same • No clinical or cost differences for treatments after menopause • Patients with first-line treatment failure receive second-line treatment with an alternative, more invasive procedure • QoL assumed to be the same for all successful treatments and assumed not to change beyond 6 months post treatment • 3.5% discount rate
Wu 2007 (HOPEFUL), United Kingdom[48]	Cost-utility analysis United	UAE, hysterectomy	Premenopausal women (aged 44 to 55 years) with symptomatic	11 years (until menopause, at age 55)	• Women undergo menopause at age 55 • Patients with UAE

First Author, Publication Year, Country	Type of Analysis, Perspective	Intervention and Comparator(s)	Study Population	Time Horizon	Main Assumptions
Funded by the UK Department of Health	Kingdom public-payer perspective		uterine fibroids		failure would have additional procedures (UAE, myomectomy, or hysterectomy) • 3.5% discount rate
Beinfeld 2004, United States[49] Portions funded by the US Department of the Army	Cost-utility analysis Societal perspective	UAE, hysterectomy, no treatment	Premenopausal women (aged 40 to 51 years) with symptomatic uterine fibroids	11 years (until menopause, at age 51)	• Women reach menopause at age 51 • No clinical or cost differences for treatments after menopause • Patients with UAE failure would undergo hysterectomy within 30 days • Patients with UAE followed by symptom recurrence would undergo hysterectomy within 1 year • Assumed annual recurrence rate of 0.00 based on expert opinion • Utilities after a successful UAE were assumed to be the same as women in the same age group in the general population • 3% discount rate

MRgFU = magnetic resonance-guided focused ultrasound; MRI = magnetic resonance imaging; NIH = National Institutes of Health; QALY = quality-adjusted life-year; QoL = quality of life; UAE = uterine artery embolization.

Appendix 9: Economic Evidence — Critical Appraisal of Studies

Table 9-1: Strengths and Limitations of Economic Studies Using Drummond[70]

Strengths	Limitations
Babashov 2015[43]	
• Research question is clearly stated with its economic importance given the regional context • Viewpoints of the analysis clearly defined and justified • Clearly described interventions and comparators with appropriate rationale for inclusion • Choice of economic evaluation and primary outcome measures are clear and justified • Sources of natural history model parameters (treatment eligibility, efficacy, safety) clearly referenced and described (with study design and results, or methods of synthesis, where warranted) • Methods to value benefits stated • Unit costs and quantities of resources used described clearly and separately • Currency and price data are recorded • Markov model structure and key parameters well described and appropriate • Time horizon stated and adequately captures relevant consequences of treatment • Discount rate stated and justified • Appropriate approaches to scenario and sensitivity analyses used and clearly described • Uncertainty in utilities addressed in sensitivity analysis • Results are clearly described (aggregated and disaggregated form) and the research question is adequately addressed • Conclusions clearly follow the reported data and include appropriate caveats	• Utilities derived from a single study that differed from those reported in other, similar publications • Assumed that post-discharge, patients would not experience complications associated with significant costs • Details of statistical tests and confidence intervals not provided in the stochastic analysis • Unclear whether uncertainty in the costing parameters was explored adequately
Cain-Nielsen 2014[44]	
• Research question and associated economic importance is given • Viewpoint of the analysis clearly defined • Clearly described interventions and comparators with appropriate rationale for inclusion • Choice of economic evaluation and primary outcome measures are clear and justified • Sources of model parameters derived from multiple studies (treatment eligibility, efficacy, safety, costs) clearly referenced and described with methods of synthesis • Methods to value benefits and sources of utilities stated • Lost productivity costs reported separately from initial base-case analysis • Currency and price data are recorded • Method of price adjustment for inflation stated • Markov model structure and key parameters well	• Details of design and results of single studies used to inform model parameter estimates not provided • Quantities of resource use not described separately from costs • Costs of complications not previously published, based on assumption that top 25% of costliest patients would include cost of major complications • Time horizon limited to 5 years

Strengths	Limitations
described and appropriate • Time horizon stated • Discount rate stated and justified • Distribution details for model parameters provided • Appropriate approaches to scenario and sensitivity analyses used and clearly described • Uncertainty in utilities and costs addressed in sensitivity analysis • Results are clearly described (aggregated and disaggregated form) and the research question is adequately addressed • Conclusions clearly follow the reported data and include appropriate caveats	
Kong 2014[45]	
• Research question and associated economic importance is given • Viewpoint of the analysis stated • Clearly described interventions and comparators with appropriate rationale for inclusion • Choice of economic evaluation and primary outcome measures are clear and justified • Source of effectiveness estimates stated • Methods to value benefits and estimate costs stated • Lost productivity costs reported separately • Currency conversion described, where applicable • Model structure and key parameters well described and appropriate • Time horizon and discount rate stated • Approach to sensitivity analyses described • Uncertainty in costs and utilities addressed in sensitivity analysis • Results are clearly described (aggregated and disaggregated form) and the research question is adequately addressed • Conclusions clearly follow the reported data and include appropriate caveats	• Myomectomy not included as a first-line treatment option, evaluated only as a second-line option to UAE without explanation • Methods for pooling multiple model parameter estimates not provided • Details and results of single studies supporting model parameter estimates not provided • Patients from whom utilities were obtained not described in detail • Quantities of resource use not described separately from costs • Details of statistical tests and confidence intervals not provided in the stochastic analysis • Sensitivity analysis not performed for effectiveness parameters if base-case estimate was derived from a single study (ranges for sensitivity analyses were derived from multiple studies)
O'Sullivan 2009[4]	
• Research question and associated economic importance is given • Viewpoint of the analysis stated • Clearly described interventions and comparators with appropriate rationale for inclusion • Choice of economic evaluation and primary outcome measures are clear and justified • Source of effectiveness estimates stated • Methods to value benefits and estimate costs stated • Lost productivity costs reported separately and discussed • Currency and price data are recorded • Markov model structure and key parameters well	• Methods for synthesizing multiple model parameter estimates not provided • Details and results of single studies supporting model parameter estimates not provided • Patients from whom utilities were obtained not described in detail • Quantities of resource use not described separately from costs • Details of statistical tests and confidence intervals not provided in the stochastic analysis

Strengths	Limitations
described and appropriate • Time horizon and discount rate stated • Appropriate approaches to scenario and sensitivity analyses used and clearly described • Results are clearly described (aggregated and disaggregated form) and the research question is adequately addressed • Conclusions clearly follow the reported data and include appropriate caveats	
Hirst 2008 (HOPEFUL)[46]	
• Research question and associated economic importance is given • Viewpoints of the analysis clearly defined and justified • Clearly described interventions and comparators • Choice of economic evaluation and primary outcome measures are clear and justified • Source of most model parameter estimates from a single study (HOPEFUL study) stated and associated details of study design and results provided • Sources of model parameters derived from multiple studies (e.g., technical failure) clearly referenced and methods of synthesis provided • Methods to value benefits stated • Details of patients from whom utilities were obtained were provided • Productivity loss costs reported separately • Methods to estimate costs described • Currency and price data are recorded • Model structure and key parameters well described and appropriate • Time horizon and discount rate stated • Sensitivity analyses clearly described • Results are clearly described and the research question is adequately addressed • Conclusions clearly follow the reported data and include appropriate caveats	• Myomectomy discussed as an alternative surgical option to hysterectomy but not included as comparator in economic analysis • Costs associated with productivity loss are presented but relevance of these cost changes to the study question not discussed • Quantities of resource use not described separately from costs • Several variables not assessed in sensitivity analyses (e.g., range of probabilities for treatment effectiveness, complications, utilities) • Details of statistical tests and confidence intervals not provided for stochastic data • Incremental analysis not consistently reported
Zowall 2008[47]	
• Research question and associated economic importance is given • Viewpoints of the analysis clearly defined and justified • Clearly described interventions and comparators • Choice of economic evaluation and primary outcome measures are clear and justified • Methods to value benefits and estimate costs stated • Currency and price data are recorded • Markov model structure and key parameters described and appropriate • Time horizon and discount rate stated • Approach to sensitivity analysis is given and reasonable	• Methods for pooling multiple model parameter estimates not provided • Details and results of single studies supporting model parameter estimates not provided • Details of patients from whom utilities were obtained not provided • Quantities of resource use not described separately from costs • Details of statistical tests and confidence intervals not provided for stochastic data

Strengths	Limitations
• Results are clearly described (aggregated and disaggregated form) and the research question is adequately addressed • Conclusions clearly follow the reported data and include appropriate caveats	
Wu 2007[48]	
• Research question and associated economic importance is given • Viewpoints of the analysis clearly defined and justified • Clearly described interventions and comparators • Choice of economic evaluation and primary outcome measures are clear and justified • Source of most model parameter estimates from a single study (HOPEFUL study) stated and reference provided for further details • Methods to value benefits stated • Productivity loss costs reported separately • Methods to estimate costs described • Currency and price data are recorded • Model structure and key parameters well described and appropriate • Time horizon and discount rate stated • Sensitivity analyses clearly described • Results are clearly described and the research question is adequately addressed • Conclusions clearly follow the reported data and include appropriate caveats	• Myomectomy presented as a treatment option after failure but not included as comparator in economic analysis • Methods of synthesis for model parameter estimates derived from multiple studies (e.g., technical failure) not provided • Costs associated with productivity loss are presented, but relevance of these cost changes to the study question not discussed • Quantities of resource use not described separately from costs • Several variables not assessed in sensitivity analyses (e.g., range of probabilities for treatment effectiveness, complications, utilities) • Details of statistical tests and confidence intervals not provided for stochastic data • Incremental analysis not consistently reported
Beinfeld 2004[49]	
• Research question and associated economic importance is given • Viewpoints of the analysis clearly defined and justified • Clearly described interventions and comparators • Choice of economic evaluation and primary outcome measures are clear and justified • Source of model parameter estimates (probabilities, costs, utilities) stated • Methods to estimate costs described • Currency and price data are recorded • Details for currency conversion given • Model structure and key parameters well described and appropriate • Time horizon and discount rate stated • Sensitivity analyses clearly described and appropriate • Results are clearly described (aggregated and disaggregated form) and the research question is adequately addressed • Conclusions clearly follow the reported data and include appropriate caveats	• Details and results of single studies supporting model parameter estimates not provided • Details of patients from whom utilities were obtained not provided • Productivity changes and associated costs not reported separately • Quantities of resource use not described separately from costs • Details of statistical tests and confidence intervals not provided for stochastic data

HOPEFUL = the Hysterectomy Or Percutaneous Embolisation for Uterine Leiomyomata study; UAE = uterine artery embolization.

Appendix 10: Economic Evidence — Study Results

Table 10-1: Summary of Findings of Included Economic Evaluations

Main Study Findings	Author's Conclusions
Babashov 2015[43]	
Base case (hysterectomy reference) • UAE vs. hysterectomy, ICER = $46,480/QALY • Myomectomy strictly dominated by all other interventions (higher costs, lower QALYs) • MRgFU extendedly dominated by a combination of UAE and hysterectomy Scenario 1 (uterine-preserving treatment options only; MRgFU reference) • UAE vs. MRgFU, ICER = $46,495/QALY • Myomectomy strictly dominated by all other interventions Scenario 2 (all patients eligible for MRgFU; hysterectomy reference) • MRgFU vs. hysterectomy, ICER = $32,757/QALY • UAE vs. MRgFU, ICER = $70,239/QALY • Myomectomy strictly dominated by all other interventions Scenario 3 (all patients eligible for MRgFU, and UAE is not available; hysterectomy reference) • MRgFU vs. hysterectomy, ICER = $39,254/QALY • Myomectomy strictly dominated by all other interventions One-way sensitivity analyses: • UAE was the cost-effective option for most scenarios when the WTP threshold was $50,000/QALY and $100,000/QALY. At a WTP threshold of $50,000/QALY, MRgFU became the cost-effective strategy when the utility of symptomatic fibroid was high, utility of symptomatic relief was low, cost of MRgFU was low, probability of recurrence with MRgFU was low, or the proportion of patients eligible for MRgFU was high. At a $100,000/QALY WTP threshold, MRgFU was the • cost-effective strategy when the probability of recurrence with UAE was high or the probability of recurrence with MRgFU was low.	From a Canadian public-payer perspective, UAE was the most cost-effective treatment option for women with symptomatic uterine fibroids, unless all patients are eligible for MRgFU. MRgFU becomes the most cost-effective treatment option when all women are eligible and UAE is not available. Myomectomy was not cost-effective in any of the tested scenarios.
Cain-Nielsen 2014[44]	
Base case (myomectomy reference, WTP threshold of $50,000/QALY; ICERs above the threshold are cost-effective) • Productivity costs excluded: MRgFU vs. myomectomy, ICER = $46,250/QALY • Productivity costs included: MRgFU vs. myomectomy,	From an American societal perspective, myomectomy was found to be the most cost-effective treatment option when productivity costs are not considered; MRgFU is the most cost-effective option when productivity costs are included. However, due to uncertainty in the model

Main Study Findings	Author's Conclusions
ICER = $341,750/QALY • UAE dominated in both scenarios One-way sensitivity analyses • Preferred treatment strategy was sensitive to several parameters, both when productivity costs were included and excluded from the model • All treatment strategies preferred in certain circumstances Probabilistic sensitivity analyses • Model sensitive to parameter uncertainty • Including direct costs only: MRgFU preferred when WTP threshold $15,000/QALY to $25,000/QALY (in approximately 36% of iterations); myomectomy preferred at all other values (ranges from 36% to 40% of iterations) • Low productivity costs included: UAE preferred at WTP threshold under $30,000/QALY (ranges from 43% to 35% of iterations), MRgFU preferred at $30,000/QALY to $105,000/QALY, myomectomy preferred above $105,000/QALY (for both, probability in which treatment is cost-effective ranges near 35 to 36%)	and depending on variations in WTP thresholds, all 3 strategies may be cost-effective for the treatment of symptomatic uterine fibroids.
Kong 2014[45]	
Base case (hysterectomy reference) • MRgFU vs. hysterectomy, ICER = $33,110/QALY • UAE vs. MRgFU, ICER = $270,057/QALY • Re-intervention rates: 93/100 for MRgFU, 71/100 for UAE • Complication rates: 37/100 for hysterectomy, 16/100 for UAE, 12/100 for MRgFU Sensitivity analysis (increasing patient age at treatment start) • ICER for MRgFU improves as age increases from 40 to 49 • UAE dominated by MRgFU at all ages above 41 • UAE the preferred strategy when probability of symptom relief with MRgFU was below 74% or when base cost of MRgFU was above 200% • Hysterectomy the preferred strategy when probability of fibroid recurrence after UAE above 4.7% • Hysterectomy dominated MRgFU when the utility value for symptomatic fibroids was lower	From an American societal perspective, MRgFU was a cost-effective first-line treatment for symptomatic uterine fibroids, and becomes more cost-effective as patient age increases.
O'Sullivan 2009[4]	
Base case (pharmacotherapy reference) • Hysterectomy vs. pharmacotherapy, ICER = $21,800/QALY • MRgFU vs. hysterectomy, ICER = $41,400/QALY • UAE vs. MRgFU, ICER = $54,200/QALY	From an American societal perspective, MRgFU is cost-effective at the generally accepted WTP threshold of $50,000/QALY.

Main Study Findings	Author's Conclusions
• Myomectomy strictly dominated One-way sensitivity analyses • MRgFU was cost-effective in most scenarios when the WTP threshold was $50,000/QALY • UAE was cost-effective in most scenarios when the WTP threshold was $100,000/QALY • ICERs and most cost-effective treatment choices at each WTP threshold were most sensitive to the probability of symptom relief, probability of symptom recurrence, and procedure costs for UAE and MRgFU • ICERs from reference case analysis (productivity costs omitted from cost estimates) and alternative analyses (less conservative estimates for complications rates and costs, recurrence rates, eligibility rate for MRgFU) provided the same or similar conclusions as the base case • Myomectomy was always dominated by the other treatment strategies	
Hirst 2008[46]	
Base case (age at initial treatment 44 years) • UAE had lower costs (£1,769 vs. £3,462) and higher QALYs (0.820 vs. 0.815) than hysterectomy within the first year of treatment • UAE incurred additional costs (£907) while hysterectomy did not, and UAE had lower QALYs (7.384 vs. 7.426) in the subsequent years after treatment • When capturing the complete time horizon, UAE was less costly but less effective than hysterectomy Alternate analysis (age at initial treatment 35 years) • Same results as the base case were observed for the first year following treatment • UAE incurred greater costs (overall difference £138) and fewer QALYs (overall difference 0.081) than hysterectomy in subsequent years after treatment • When capturing the complete time horizon, UAE was more costly but less effective than hysterectomy One-way sensitivity analyses • UAE dominant when incremental utility associated with retaining a uterus was applied • Reduction in procedural success rate for young women (younger than 30 years with less severe symptoms) revealed that UAE is more cost-effective than no treatment (ICER = £4,280/QALY) • Inclusion of lost productivity costs increased the cost difference from the base case between UAE and hysterectomy (£907 to £2,805)	From a UK public-payer perspective, UAE has lower costs and is more effective than hysterectomy within the first year of treatment for symptomatic uterine fibroids. However, this result is not maintained in subsequent years after treatment. UAE is not preferred in younger patients who may require treatment over a longer period of time, but may be a cost-effective option for women who wish to preserve their uterus.

Main Study Findings	Author's Conclusions
Probabilistic sensitivity analysis • In general, UAE is associated with lower costs and similar QALYs to hysterectomy • Overall, UAE is more cost-effective than hysterectomy when WTP threshold is less than £30,000/QALY	
Zowall 2008[47]	
Base case (25% UAE, 25% myomectomy, 50% hysterectomy) • MRgFU is dominant Sensitivity analyses MRgFU remains dominant under the following scenarios with alternate assumptions: • Adjusted distribution of initial treatment between UAE, myomectomy, and hysterectomy • Alternate utility values after hysterectomy • Decreased rates of recurrence for all other procedures • Long-term complications for all other treatments are reduced to 0 • MRgFU complication rate set to equal that of UAE • Death rates of all other treatments reduced to 0 MRgFU not dominant under the following scenarios: • Costs of all other procedures set to lower quartile hysterectomy cost (£2,054); ICER = £27,845/QALY • Increased initial hospital costs of MRgFU to £2,630; ICER = £33,685/QALY • MRgFU is the dominant strategy until age 43 • MRgFU is dominant in 86% of probabilistic sensitivity analyses	From a UK public-payer perspective, MRgFU is a cost-effective treatment strategy for symptomatic uterine fibroids compared with UAE, myomectomy, and hysterectomy. This result is consistent for analyses with alternate assumptions regarding clinical practice, utilities, and clinical effectiveness. The outcomes of the model are sensitive to treatment costs and age of the patients.
Wu 2007[48]	
Base case (age at initial treatment 44 years) • UAE had lower costs (£1,677 vs. £3,282) and higher QALYs (0.820 vs. 0.815) than hysterectomy within the first year of treatment • UAE incurred additional costs (£860) while hysterectomy did not, and UAE had lower QALYs (7.384 vs. 7.426) in the subsequent years after treatment • When capturing the complete time horizon, UAE was less costly but less effective than hysterectomy Alternate analysis (age at initial treatment 35 years) • Same results as the base case were observed for the first year following treatment • UAE incurred greater costs (overall difference £129) and fewer QALYs (overall difference 0.081) than hysterectomy in the subsequent years after treatment • When capturing the complete time horizon, UAE was more costly but less effective than hysterectomy	From a UK public-payer perspective, UAE has lower costs and is more effective than hysterectomy within the first year of treatment for symptomatic uterine fibroids. However, this result is not maintained in subsequent years after treatment. UAE is not preferred in younger patients who may require treatment over a longer period of time, but may be a cost-effective option for women who wish to preserve their uterus.

Main Study Findings	Author's Conclusions
One-way sensitivity analyses • UAE dominant when utility associated with retaining a uterus was applied • Reduction in procedural success rate for young women (younger than 30 years with less severe symptoms) revealed that UAE is more cost-effective than no treatment (ICER = £4,100/QALY) • Inclusion of lost productivity costs increased the cost difference from the base case between UAE and hysterectomy (£746 to £2,687) Probabilistic sensitivity analysis • In general, UAE is associated with lower costs and similar QALYs to hysterectomy	
Beinfeld 2004[49]	
Base case (no treatment as reference) • UAE vs. no treatment, ICER = $2,007/QALY • UAE dominated hysterectomy Sensitivity analyses • ICERs for all scenarios of UAE vs. no treatment were under $16,000/QALY • UAE was more effective and more expensive than no treatment, except when the patients were younger than 30 and when no QoL adjustments were made • UAE dominated hysterectomy except when cure rate of UAE was reduced to 75%, procedural costs or recovery time were increased, or post-hysterectomy recovery time was reduced • The model was sensitive to post-treatment utility adjustments	From an American societal perspective, UAE is a cost-effective alternative to hysterectomy for the treatment of symptomatic uterine fibroids. The results were consistent among changes to several model parameters, but were sensitive to assumptions about QoL.

ICER = incremental cost-effectiveness ratio; MRgFU = magnetic resonance-guided focused ultrasound; QALY = quality-adjusted life-year; QoL = quality of life; UAE = uterine artery embolization; vs. = versus; UK = United Kingdom; vs. = versus; WTP = willingness-to-pay.