



# Effective Health Care Program

## Management of Uterine Fibroids

### Evidence Summary

#### Introduction

Uterine fibroids (i.e., leiomyomata) are common benign smooth muscle tumors of the uterus. Most women will develop one or more uterine fibroids during their reproductive lifespan.<sup>1</sup> In the United States, an estimated 26 million women between the ages of 15 and 50 have uterine fibroids.<sup>1-4</sup> More than 15 million of them will experience associated symptoms or health concerns.<sup>5,6</sup> On average, African American women are younger at onset of fibroids, and have larger and more numerous tumors.<sup>1,3</sup> They are also more likely to have surgical interventions for fibroids.<sup>7</sup> Over the reproductive lifetime prevalence becomes more similar so that by age 49, more than 70 percent of white women and 84 percent of African American women have fibroids documented by imaging or surgical records.<sup>1</sup>

The personal and societal costs of diminished quality of life, disruption of usual activities and roles, lost work time, and healthcare expenditures are substantial. Including all types of interventions, direct annual healthcare costs in the United States are projected to exceed \$9.4 billion.<sup>8</sup> Lost wages, productivity, and short-term disability are estimated to total more than \$5 billion, perhaps as much as \$17 billion, with roughly \$4,624 in costs per woman in the first year of diagnosis.<sup>8,9</sup>

#### Purpose of Review

To review treatment effectiveness and the risk of leiomyosarcoma (LMS) in women with fibroids.

#### Key Messages

- Gonadotropin-releasing hormone (GnRH) agonists, mifepristone, ulipristal, and uterine artery embolism (UAE) reduce fibroid size, and improve symptoms and quality of life. High intensity focused ultrasound reduces fibroid size, but impact on quality of life was not measured. Myomectomy and hysterectomy also improve quality of life. Direct comparisons of interventions provide little evidence.
- For women in their 30s, the chance of needing retreatment for fibroids within the next 2 years was 6–7 percent after medical treatment or myomectomy and 44 percent after UAE. For older women, the chance was 9–19 percent after medical treatment or UAE and 0 percent after myomectomy.
- Using data from 160 studies, risk of unexpected LMS ranged from less than 1 to 13 of 10,000 surgeries.
- Survival time appears shorter with power morcellation; however, confidence intervals are wide and overlap with other surgical approaches.



Treatment options differ in fundamental aspects such as cost, invasiveness, recovery time, risks, likelihood of long-term resolution of symptoms, need for future care for fibroids, and influence on future childbearing. Thus synthesis of available evidence is crucial to assist women and their care providers in making well-informed and personalized decisions.

One concern affecting surgical treatment is the risk of discovering a leiomyosarcoma, a cancer of the uterine muscle, rather than a fibroid at surgery. These are rare but ominous: an average of 1,600 new cases occur in the United States each year. They have poor outcomes with an average 5-year survival of 36 percent if cancer is not isolated to the uterus.

## Scope

To inform clinical decisions about care we focused on evidence from randomized controlled trials (RCTs) that assess currently available interventions for women of any age with fibroids. We also sought to identify factors that might influence likelihood of favorable results or harms from treatments. We included studies evaluating medications (including intrauterine devices [IUDs] as they deliver medication), procedures, and surgeries for the management of uterine fibroids. We considered more invasive interventions that are typically performed in an operating room or require at least a brief hospital stay as surgical and interventions that can typically be conducted in an office or as same-day surgery as procedures.

We also summarized data from women who were followed within trials without active intervention. In light of recent uncertainty about the risk of cancer dissemination following morcellation of fibroids, this review also includes literature to estimate the prevalence of leiomyosarcoma and influence of morcellation on survival in women with leiomyosarcoma.

## Key Questions

**Key Question 1. What is the comparative effectiveness (benefits and harms) of treatments for uterine fibroids, including comparisons among these interventions?**

**Key Question 2. Does treatment effectiveness differ by patient or fibroid characteristics (e.g., age; race/ethnicity; symptoms; menopausal status; imaging characteristics; vascular supply to fibroids; or number, size, type, location, or total volume of fibroids)?**

**Key Question 3. What is the risk of encountering a leiomyosarcoma for masses believed to be uterine fibroids at the time of myomectomy or hysterectomy?**

**Key Question 4. Does survival after leiomyosarcoma differ by patient or fibroid characteristics (e.g., age; race/ethnicity; symptoms; menopausal status; imaging characteristics; vascular supply to fibroids; or number, size, type, location, or total volume of fibroids) or by surgical approach to morcellation?**

## Methods

We searched MEDLINE® via PubMed® and Embase® to identify publications in English from January 1985 to September 2016. We also checked the reference lists of included studies. We dually reviewed each publication against a priori inclusion/exclusion criteria. For Key Question (KQ) 1 and KQ2, we identified RCTs to assess benefits or harms of medical, procedural, or surgical interventions compared with an alternative intervention or inactive control, including expectant management, placebos, or sham procedures. Eligible studies for KQ1 or KQ2 had to report one or more patient-centered outcomes or fibroid characteristics at baseline and in followup (e.g., symptom improvement, bleeding pattern, pain, quality of life). We did not present studies reporting only intermediate outcomes such as technical success, conversion to alternate procedure, estimated blood loss during procedure, wound healing status, length of stay, and readmission or reoperation, except in the discussion of specific harms (see analytic framework in full report).

We extracted data, assessed risk of bias, and rated the strength of the evidence for informing care using standard Agency for Healthcare Research and Quality (AHRQ) systematic review methods. We used followup data across all trials of medical management, UAE, or myomectomy that included subsequent treatment to estimate probabilities of selecting subsequent treatment. The probability of the occurrence of subsequent treatment events was estimated using a Poisson model, where the rate of occurrence was assumed to be a function of patient age and study followup time, on a logarithmic scale.

To understand risk of leiomyosarcoma and the influence of morcellation on survival (KQ3 and KQ4) we conducted dual review and data extraction from observational studies, and trials with relevant data. Our models included the effect of the mean age of women in each study and the year in which it was published as candidate covariates and we stratify by prospective versus retrospective study

design. For KQ3, we structured a search to encompass the papers included in a 2015 review and meta-analysis<sup>10</sup> that estimated the prevalence of leiomyosarcoma among tumors presumed to be fibroids. We updated the search, used comparable eligibility criteria, and calculated new estimates for the prevalence of leiomyosarcoma identified at the time of surgery for presumed fibroids including both the prior studies and newly identified papers. To be included, papers were required to provide data to calculate the proportion of surgeries for fibroids that revealed leiomyosarcoma. We calculated meta-estimates of the probability of leiomyosarcoma for all relevant studies and by study characteristics.

For KQ4 we conducted a broad search and reviewed potentially eligible papers for those that included data about leiomyosarcoma diagnosis and survival as well as the proportion of women exposed to morcellation who were subsequently diagnosed with leiomyosarcoma or disseminated leiomyosarcoma (meaning presence or recurrence of leiomyosarcoma beyond the initial operative tissue specimen). We extracted data to allow comparison of survival for three groups: those with power morcellation, those with sharp (scalpel) morcellation, and those with no morcellation (the uterus was removed intact). We generated Kaplan-Meier survival curves using event times when they were available in order to compare survival time by method of surgical removal of the specimen.

## Results

The first AHRQ systematic review on the management of uterine fibroids was published in 2001 and included 30 randomized trials of interventions to treat fibroids.<sup>11</sup> A more recent AHRQ review in 2007 identified 29 additional trials.<sup>12</sup> Across reviews, most studies had poor quality and typically reported only on technical success of the intervention with abbreviated followup of outcomes. Longer-term outcomes such as quality of life, fertility, sexual function, improvement in symptoms and satisfaction with care were rarely reported. These reviews served to answer key questions about epidemiologic correlates of fibroids, to demonstrate lack of evidence about natural history of disease, provided models of lifetime incidence and need for treatment and included cohort studies as a surrogate for trials to examine preliminary evidence of effectiveness and predictors of outcomes.

In the intervening years, the literature has grown to include 121 publications from 97 unique trials (see main report for full reference list). Newer studies have been of somewhat higher quality—18 in this report were judged good quality trials, 27 fair, and 52 poor quality. More interventions

have been assessed for longer followup periods, up to 5 years. Patient-reported outcomes are more common, reported in 63 percent of studies, as are data to determine what sequences of interventions are most likely to be chosen subsequently by women with reference to their prior treatment allocation in trials (48 studies). More trials also provide more data to examine whether particular desired outcomes are more likely to be achieved among women with specific characteristics. Six studies provided information about factors such as age, menopausal status, and fibroid characteristics that may modify outcomes or risk of adverse events.

Clinical trials are not powered to detect harms. To address the current pressing concerns of potential for cancer dissemination at the time of surgery for fibroids, we identified a separate literature of 160 publications to examine risk that a mass believed to be a fibroid was found to be a leiomyosarcoma. We also sought data within 28 papers that allowed estimation of the risk of progression of leiomyosarcoma by type of morcellation used, estimating aggregate mortality by surgical methods used. Lastly, we combed these papers for data about whether characteristics of women or the masses believed to be fibroids were associated with leiomyosarcoma presence or modified the likelihood that morcellation during a surgery for fibroids would be associated with harm.

### KQ1: Effectiveness of Treatments for Fibroids

The included RCTs reported effectiveness more often than harms. We summarize our results below by category of intervention, providing data about adverse events when available and statistically informative. We categorized interventions using the publication authors' description. Interventions include expectant management or placebo; medications to improve or resolve symptoms or reduce size of fibroids (including those delivered via IUDs); procedures (uterine artery occlusion via embolization, ligation, or coagulation; and fibroid ablation (e.g., high intensity focused ultrasound, radiofrequency); and surgery (including endometrial ablation; hysterectomy via abdominal, vaginal, and laparoscopic approaches and those with robotic assistance; and myomectomy via laparotomy, laparoscopy, hysteroscopy, or with robotic assistance).

### Evidence Map for KQ1

We summarize the number of studies reporting final health outcomes, number of participants and duration of followup for medications (Table A), procedures (Table B), and surgeries (Table C). Complete outcomes data are available in the Systematic Review Data Repository.

**Table A. Final health outcomes reported in medication studies**

<b>Intervention</b>	<b>Outcome Category</b>	<b>Studies Reporting N</b>	<b>Baseline Participants N</b>	<b>Duration of Followup, Range in Months<sup>a</sup></b>
GnRH Agonists <sup>b</sup>	Symptom status	13	785	<1 to 36
	Sexual function	1	60	0
	Fibroid characteristics	18	912	<1 to 36
	Subsequent treatment for fibroids	1	51	6
Progesterone Receptor Agents <sup>c</sup> (mifepristone, ulipristal, levonorgestrel IUD)	Symptom status	18	1,916	0 to 18
	Pregnancy outcomes	1	220	9
	Sexual function	1	220	9
	Fibroid characteristics	18	1,916	0 to 18
	Subsequent treatment for fibroids	8	1,224	3 to 12
Estrogen Receptor Agents <sup>d</sup> (raloxifene, tamoxifen, HRT)	Symptom status	6	201	2 to 60
	Fibroid characteristics	6	201	2 to 60
	Subsequent treatment for fibroids	1	10	60
Other Medications (cabergoline, tranexamic acid, tibolone)	Symptom status	3	178	0.23 to 3
	Fibroid characteristics	2	55	0.23
	Subsequent treatment for fibroids	1	30	0.23

GnRH = gonadotropin-releasing hormone; HRT = hormone replacement therapy; IUD = intrauterine device; N = number

<sup>a</sup>Duration of followup is defined as months elapsed from end of active treatment to evaluation of outcome(s)

<sup>b</sup>Includes only those GnRH studies discussed in the GnRH report section

<sup>c</sup>Anti-progestins, selective receptor modulators, and levonor-gestrel IUD

<sup>d</sup>Selective receptor modulators, antagonists, and HRT (transdermal estradiol plus cyclic oral medroxyprogesterone acetate)

**Table B. Final health outcomes reported in studies of procedures**

<b>Intervention</b>	<b>Outcome Category</b>	<b>Studies Reporting N</b>	<b>Baseline Participants N</b>	<b>Duration of Followup, Range in Months<sup>a</sup></b>
Uterine Artery Embolization	Symptom status	14	963	3 to 60
	Fibroid characteristics	21	1204	3 to 60
	Subsequent treatment for fibroids	11	784	6 to 60
	Satisfaction with outcomes	8	584	6 to 60
Radiofrequency Fibroid Ablation	Symptom status	2	76	0 to 24
	Fibroid characteristics	2	76	0 to 24

**Table B. Final health outcomes reported in studies of procedures (continued)**

<b>Intervention</b>	<b>Outcome Category</b>	<b>Studies Reporting N</b>	<b>Baseline Participants N</b>	<b>Duration of Followup, Range in Months<sup>a</sup></b>
High Intensity Focused Ultrasound for Fibroid Ablation <sup>b</sup>	Symptom status	2	53	1 to 24
	Sexual function	1	50	<1
	Fibroid characteristics	5	216	1 to 24

N = number

<sup>a</sup>Duration of followup is defined as months elapsed from procedure to evaluation of outcome(s)

<sup>b</sup>High intensity focused ultrasound includes procedures guided by magnetic resonance imaging

**Table C. Final health outcomes reported in surgical studies**

<b>Intervention</b>	<b>Outcome Category</b>	<b>Studies Reporting N</b>	<b>Baseline Participants N</b>	<b>Duration of Followup, Range in Months<sup>a</sup></b>
Endometrial Ablation	Symptom status	1	96	12
	Subsequent treatment for fibroids	1	96	12
Myomectomy	Symptom status	4	285	3 to 24
	Pregnancy outcomes	5	447	12 to 36
	Sexual function	1	52	6
	Fibroid recurrence	5	494	6 to 40
	Subsequent treatment for fibroids	3	219	24 to 36
	Satisfaction with outcomes	4	339	3 to 24
Hysterectomy	Symptom status	1	30	24
	Satisfaction with outcomes	5	317	1 to 24
Hysterectomy or Myomectomy	Symptom status	2	71	12 to 60
	Pregnancy outcomes	1	20	12
	Fibroid characteristics	1	51	60
	Subsequent treatment for fibroids	2	115	12 to 60
	Satisfaction with outcomes	2	115	12 to 60

N = number

<sup>a</sup>Duration of followup is defined as months elapsed from surgery to evaluation of outcome(s)

To synthesize anticipated effects of interventions based on this literature, we group trial arms in text and tables to be able to describe outcomes of those interventions together. Throughout this report, we refer to whether or not a study assessed change in specific measures including fibroid characteristics like size or volume, symptoms (bleeding or pain), and quality of life. Indicating the study assessed *change* means it evaluated the characteristic or symptom at baseline and again at one or more times after treatment. Noting that a study or studies assessed change is not equivalent to noting a beneficial effect or statistical significance in changes. Rather, noting measurement of change in a parameter establishes the total count of studies that addressed this outcome.

### **Expectant Management**

We did not identify any studies intentionally designed to determine outcomes of no intervention, also called expectant management or watchful waiting. However, 16 small RCTs compared a treatment to no intervention, typically trials that compared a medication with placebo. Of these trials two were of good quality, six were fair, and eight were poor quality. The evidence, based on an average followup time of five months (range: 3 to 12 months), suggests the size of fibroids does not meaningfully change over these short timespans. One study reported a four percent reduction in size and those that reported volume measures documented an average increase in size of about 9 cm<sup>3</sup>, which is about one-fifth the size of a golf ball. The two studies that followed postmenopausal women for a full year did not detect an increase in total volume of fibroids.

Likewise, bleeding characteristics, such as days of bleeding and severity of bleeding as measured by hemoglobin, heaviness of periods, and severity of heavy bleeding episodes, did not change meaningfully during followup for those without active management. The proportion of the 514 women enrolled in these trials who presented specifically with problem bleeding, as opposed to other fibroid-related symptoms, is not known. However, the data suggests that women with fibroids should not expect that bleeding patterns will worsen over the near term.

**Summary/Strength of Evidence (SOE):** None of these studies were designed to evaluate expectant management. The number of women in the literature followed without intervention is small, and these participants may be fundamentally different from other women with fibroids since they were willing to risk randomization to no intervention. For these reasons, the evidence is insufficient to inform choice of expectant management over other options.

### **Medical Management**

We identified 43 studies assessing effectiveness of medical treatment (including progesterone delivered by IUD) for uterine fibroids. Ten studies had placebo or no treatment comparison groups. Approximately one third were industry sponsored. The longest duration of followup after the end of treatment was 60 months in one study. Women included in the studies were predominately premenopausal (39 studies). Four studies evaluated therapies in postmenopausal women. We assessed four as good quality, 12 as fair quality, and 27 as poor quality for effectiveness outcomes.

#### ***GnRH (Gonadotropin-Releasing Hormone) Agonists***

Eighteen studies (reported in twenty publications) addressed GnRH agonists, which included seven studies of “add-back” therapy (addition of a second agent to a GnRH agonist). The studies included 912 participants, and followup was typically limited to the immediate end of treatment. Only six studies followed women post-treatment, for 3 to 6 months. GnRH agonists reduce the size of fibroids, with reductions in volume of fibroids documented between 64 and 175 cm<sup>3</sup> and reductions in the total volume of the uterus between 131 and 610 cm<sup>3</sup>.

Six studies reported complete absence of bleeding during treatment, three noting statistical significance for clinically important reduction from baseline. No study reported an increase in bleeding or worsening in hemoglobin or hematocrit. Individual women in several studies discontinued treatment because bleeding became more irregular or did not decrease.

Pain symptoms improved by GnRH treatment in four studies included pelvic pressure, pelvic and abdominal pain, and dysmenorrhea. Two studies reported similar improvements but without statistical comparisons of baseline to followup. Studies consistently reported significant improvement in measures of quality of life symptoms (days of bleeding, heavy menstrual bleeding, pelvic pressure, pelvic pain, urinary frequency, and constipation). Harms associated with GnRH included onset of menopausal symptoms, unfavorable changes in lipid profile, declines in cognitive function and memory, and bone loss, although some of these can be ameliorated with hormonal add-back therapy. Extended followup of women after they discontinue GnRH agonists is limited.

**Summary/SOE:** Moderate strength of evidence supports that GnRH agonists (with and without add-back therapy) reduce the size of fibroids, the overall size of the uterus, and bleeding symptoms. Low strength of evidence suggests

that fibroid-related quality of life improves with and without add-back therapy.

### ***Progesterone Receptor Agents: Anti-Progestins, Selective Receptor Modulators, and Levonorgestrel IUD***

Seven studies provided data about outcomes of the anti-progestin mifepristone treatment. Average length of time for off-medication followup was 11 months with the longest untreated followup being 18 months. All studies observed a decrease in the size of fibroids at the completion of the period of active treatment. The magnitude of change in size of the largest fibroid ranged from a decrease of 37 cm<sup>3</sup> to 95 cm<sup>3</sup>, with an average decrease of 71 cm<sup>3</sup> among the 575 women receiving mifepristone. Total uterine volume also decreased across women receiving mifepristone.

All studies of mifepristone that assessed bleeding reported reduced heaviness of bleeding. Two comparisons found mifepristone superior to placebo. Women were more or equally likely to have decreased bleeding or absent menses on the lower doses compared with the higher doses. Each of six studies that evaluated pelvic pain before and at conclusion of treatment noted substantial improvements (present in 68% to 100% at baseline compared with 9% to 28% after 3 months of treatment); findings were similar at the conclusion of 6 to 9 months of treatment and maintained post-treatment in roughly 60 percent to 90 percent of women in three RCTs with longer term followup. Four studies reporting the outcome consistently noted significant improvements in quality of life measures. Some studies suggested fibroids do resume growth after treatment. Few participants in these trials pursued other treatment during or after active treatment. Harms included spotting, elevations in liver function enzymes, and endometrial hyperplasia.

Six studies investigated treatment with ulipristal, a selective progesterone receptor modulator. All studies found ulipristal effective for reducing the size of individual fibroids and the overall fibroid burden as measured by total fibroid or uterine volume. Ulipristal, as intended, resulted in absent menses for the majority of women during treatment (range: 62% to 100%) and improved or stabilized hematocrit or hemoglobin. The exception was among women who had submucous fibroids who, in one study, had less improvement in bleeding. Compared with placebo, all ulipristal doses improved fibroid-related quality of life, and two of the six trials also documented improvement in pain. Durability of effect at 6 months was assessed in two studies: one found minimal resumption of fibroid growth (8.1%) after completion of treatment regardless

of ulipristal dose. A second found that the 10 mg dose sustained fibroid size reduction while there was increase in size on the 5 mg dose that was similar to placebo. Ulipristal was associated with hot flashes, hyperplasia, and increases in liver function enzymes, although it is not clear if these effects persist after treatment ends.

Levonorgestrel (LNG) IUD improved bleeding (the only outcome of interest reported); however, the single available trial was of poor quality including lack of participant masking.

**Summary/SOE:** There is moderate strength of evidence that both mifepristone and ulipristal effectively reduce the size of fibroids and bleeding symptoms, while improving quality of life. Duration of effects is uncertain. Evidence is insufficient to choose between higher and lower doses. Evidence was insufficient to assess the effectiveness of the LNG-IUD on any outcomes

### ***Estrogen Receptor Agents***

Six studies included agents that act at the estrogen receptor. Three studies, two of fair quality and one of poor quality, investigated raloxifene (which acts as an anti-estrogen in breast and endometrial tissue) in comparison with placebo. Fibroid size decreased by 4.4 cm<sup>3</sup> to 34.2 cm<sup>3</sup> in two studies of raloxifene and did not change size in another raloxifene study (To put this in perspective, 40 cm<sup>3</sup> is the volume of a golf ball). In raloxifene studies with premenopausal women, neither bleeding pattern (in 3 studies) nor hemoglobin levels (in one study) were improved compared with placebo. Among postmenopausal women, the percent of treatment cycles without bleeding was similar and the number of episodes of spotting and severity of bleeding were similar among women in the treated and control group.

A single poor quality study evaluated tamoxifen, which acts as an anti-estrogen within breast tissue and as an estrogen ligand in the endometrium. Tamoxifen use in premenopausal women did not influence length or severity of bleeding compared with placebo. Change in fibroid characteristics was not reported. Women receiving tamoxifen had less pain after four months of treatment compared with placebo.

Two poor quality RCTs had a total of 42 women receiving hormone replacement therapy (HRT) (transdermal estrogen replacement plus cyclic oral medroxyprogesterone acetate) after menopause. They compared hormone therapy to tibolone (not available in United States) for menopausal symptom management with attention to whether treatment increased size of fibroids. Growth was approximately 10 cm<sup>3</sup>, which is a quarter the size of a golf ball. In the

longer study there was no further growth between 6 and 12 months.

No studies reported any serious adverse effects.

**Summary/SOE:** Studies provide low strength of evidence that, if prescribed to women with fibroids for other conditions such as breast cancer prophylaxis, raloxifene will not cause significant growth of existing fibroids or exacerbate bleeding. Evidence is insufficient to assess if tamoxifen or HRT does or does not promote fibroid growth.

### Procedures for Uterine Fibroids

We identified 28 studies assessing procedures for uterine fibroids. Most studies compared similar procedures, two compared different procedures, and nine compared procedures against surgery or medications. The longest duration of followup after the end of treatment was 5 years in two studies. Participants were predominately premenopausal. We assessed 6 studies as good quality, 8 as fair quality, and 14 as poor quality for effectiveness outcomes.

### Uterine Artery Embolization (UAE) and Occlusion

We identified 21 studies that randomized women to UAE or uterine artery occlusion. We assessed five studies as good quality, eight as fair quality, and eight as poor quality for effectiveness outcomes. Fibroid and uterine volume decreased significantly and consistently following UAE (up to 12 months postprocedure) regardless of the embolization agent or size of particles used to occlude the fibroid arteries. Longer-term followup reports from the Embolization for the Treatment of Symptomatic Uterine Fibroid Tumors Study, called the EMMY Trial, confirmed that fibroid and uterine volume reductions persist up to 5 years after UAE; however, 28 percent (23/81) of women underwent subsequent hysterectomy. Subsequent treatment was reported in 11 trials with length of followup ranging from 6 to 60 months (Table 23 in the full report). Hysterectomy was the most frequent intervention (8.9%) followed by repeat embolization (4.2%), myomectomy (3.6%), medication or IUD (1.1%) and endometrial ablation (0.1%).<sup>13-23</sup>

For UAE, bleeding effects were consistent, with declines in bleeding or bleeding-related measures reported in seven studies. Pain improved in up to 84 percent of women in two studies reporting this outcome. Only eight studies of UAE measured quality of life, which consistently improved postprocedure with durability in the two studies with longer-term followup. Treatment satisfaction was high in seven studies reporting this outcome.

No women receiving UAE required transfusion. Risk of major complications during and following UAE ranged from 1.2 to 6.9 percent around the time of the procedure up to about 5 percent by 2 years. The probability of “major complications” as defined by authors was high in two studies that reported long-term followup (21% at 5 years in the Randomised comparison of uterine artery embolisation with surgical treatment in patients with symptomatic uterine fibroids Study, termed the REST Trial, and 16.8% at 32 months in a second study) in large part because they considered any subsequent procedure a complication, while other authors did not. Fertility outcomes were not evaluated in the UAE-only trials. When available, pregnancy outcomes after UAE are presented in the sections that compare UAE to other procedures or surgeries.

Trials of uterine artery occlusion were small, and a variety of intervention methods were described, which prohibits conclusions.

**Summary/SOE:** There was high strength of evidence that UAE is effective for reducing the size of fibroids and total uterine volume. Moderate strength of evidence finds that bleeding and quality of life is improved following embolization. The effect of UAE on reproductive outcomes is not well studied and evidence is insufficient to guide care or determine safety.

### High Intensity Focused Ultrasound for Fibroid Ablation

Six studies (reported in 7 publications) assessed high intensity focused ultrasound (HIFU) for fibroid ablation, but only one fair quality pilot study (n=20) used magnetic resonance imaging (MRI) guidance, which is used in the United States. The other studies were rated as poor quality primarily due to lack of masking participants and outcome assessors to the intervention received. In four studies reporting effects on fibroid size, the magnitude of fibroid volume reduction was greater at 12 months after ultrasound destruction than at 1 month post-treatment. One year after treatment fibroid volume decreased by averages of 90 and 170 cm<sup>3</sup> in two studies. Studies did not report on bleeding, pain, or pregnancy outcomes. One study addressed quality of life but did not report baseline data, and one reported improvements in sexual function. One study reported no transfusions among 48 participants. No study reported major complications.

**Summary/SOE:** HIFU reduced fibroid and uterine size, but strength of evidence is low because of short followup and poor quality of overall study design. Evidence related to patient reported outcomes is insufficient.

### ***Radiofrequency Fibroid Ablation***

Two RCTs, both assessed as poor quality, addressed radiofrequency ablation of fibroids. Both studies reported the technique was successful in delivering treatment to 5 percent or more of the targeted fibroid volume. Studies provided limited data on effects of ablation on bleeding, quality of life, and subsequent pregnancies, but did not report pain outcomes and noted no major complications.

**Summary/SOE:** The strength of evidence for radiofrequency ablation is insufficient to inform care.

### **Surgical Management**

We identified 37 randomized trials with at least one arm that assessed surgical intervention (endometrial ablation, myomectomy, or hysterectomy) for uterine fibroids. One compared myomectomy to hysterectomy, the remainder evaluated outcomes in women treated by UAE, uterine artery occlusion, HIFU, or medication. The longest duration of followup after the end of treatment was 60 months in two studies. Women included in the studies were predominately premenopausal. We assessed nine as good quality, 11 as fair quality, and 17 as poor quality for effectiveness outcomes.

### ***Endometrial Ablation***

One fair quality study addressed endometrial ablation and reported significant decreases in bleeding after both rollerball and thermal balloon ablation, with similar rates of reintervention (9%) in both groups. More women in the rollerball group had complications. More than a third of women receiving each intervention noted dissatisfaction with ablation results on a single item with three levels of satisfaction. Dissatisfaction was associated with failure to achieve amenorrhea.

### ***Myomectomy***

Fifteen RCTs reported health outcomes after myomectomy and five additional studies provided information about harms. We assessed four studies as good quality, six as fair quality, and 10 as poor quality. Studies did not report changes in fibroid characteristics (e.g., proportion of fibroids removed at myomectomy, decrease in uterine volume). One small study reported improved bleeding patterns one year after surgery in 12 of 15 women. Another described change in undefined symptoms with relief

reported by 51 of 88 women. Fibroid recurrence, reported in five studies, ranged from 2.5 percent to 25 percent with duration of followup ranging from 6 to 60 months. Two additional studies reported no recurrences at 6 month followup. Laparoscopic myomectomy was associated with faster return to usual activity than comparator surgeries in three studies and with improved quality of life compared with hysterectomy in one study. Laparoscopic myomectomy was also associated with better fertility and pregnancy outcomes over other myomectomy techniques in one study (n=136), but outcomes were comparable in another RCT (n=131). Transfusion rates were most often zero (1,040 participants in 10 studies). Six studies reported 25 transfusions among 502 participants treated by myomectomy, and seven did not report transfusion. Intraoperative conversion from myomectomy to another procedure ranged from 0 to 17 percent in eight studies (n=658). Harms associated with myomectomy included transfusion and pelvic organ injury. Harms did not differ among techniques.

**Summary/SOE:** Myomectomy is associated with improved quality of life (low strength of evidence). Since myomectomy removes fibroids, the effect on fibroid size is not measured, and strength of evidence is not graded. Evidence is insufficient to determine if myomectomy meaningfully improves bleeding patterns or anemia. Myomectomy is an option for women desiring future fertility, though evidence is insufficient to define potential benefit.

### ***Hysterectomy***

We identified 14 RCTs assessing hysterectomy (via abdominal, vaginal or laparoscopic-assisted approaches) in women with uterine fibroids. Seven reported harms only (i.e., did not report final health outcomes for effectiveness). Assessment duration (where clearly reported) in comparative studies ranged from 15 days to 24 months. We assessed five as good quality, three as fair quality, and six as poor quality for effectiveness outcomes. Among seven studies reporting health outcomes, one noted a decrease in hemoglobin postoperatively, and two reported increases in hemoglobin levels 24 months after surgery. Pain symptoms improved in three RCTs reporting outcomes of fibroid-related pain. Time to return to usual activity after hysterectomy averaged 30 to 40 days in three studies. One study reported faster recovery (mean 22 days) after laparoscopic hysterectomy. Women reported good or very good satisfaction postoperatively, though one study reported worsened physical health compared with baseline measures at 5-year followup.

The percent of women needing transfusion following hysterectomy ranged from 0 to 20 percent in 890 women from 11 studies. An event of organ perforation occurred in one study, but overall risk across studies cannot be calculated since bowel and bladder injury were not uniformly reported across studies.

**Summary/SOE:** Hysterectomy de facto reduces uterine size and bleeding; the strength of this evidence cannot be graded. There is low strength of evidence that hysterectomy improves quality of life.

### **Direct Comparisons of Interventions**

In total, 17 studies compared the effectiveness of two or more interventions. We identified four studies designed to compare outcomes across two or more of drugs (e.g., GnRH vs. ulipristal acetate). Overall these studies were small and inadequately powered for providing definitive evidence of greater effectiveness.

Two studies compared HIFU to other interventions, with greater tumor destruction after radiofrequency ablation compared with HIFU, and comparable sexual function after HIFU or myomectomy, but faster recovery in the HIFU groups.

Other direct comparisons of procedures included comparisons of UAE to myomectomy or hysterectomy. Technical success and quality of life were similar between UAE and myomectomy but reintervention rates were higher with UAE. Because of low power to detect differences, the evidence is insufficient to determine if pregnancy outcomes are better after myomectomy compared to UAE. Likewise ovarian reserve was assessed in only one study comparing UAE to hysterectomy. Symptom relief and quality of life outcomes were generally similar between UAE and hysterectomy (regardless of surgical approach), with faster recovery associated with UAE. Subsequent treatment rates were higher in the UAE group than in the hysterectomy group at each time point in followup; however, the majority of women randomly assigned to have UAE avoided hysterectomy for the duration of followup, which included 5 years of surveillance in the largest study. Fewer than one in three women with UAE required additional treatment.

**Summary/SOE:** Because of low power to detect differences, the evidence is insufficient to determine if outcomes differ in direct comparisons of procedure or medications

### **Analysis of Subsequent Treatment Following Initial Treatment for Uterine Fibroids**

From data reported in 38 studies, we estimated the probabilities of receiving additional treatment for fibroids after randomization to initial treatment with medical management, UAE, or myomectomy. For women in their 30s, the model predicted that the probability of subsequent intervention for fibroids over 2 years varied from 6 to 7 percent after medical treatment or myomectomy, to 44 percent after UAE. For women in their 40s and 50s, modelled 2-year reintervention rates were 9 to 19 percent following medical treatment or UAE, and 0 percent after myomectomy.

Overall, fewer than half of women had another intervention within 24 months. UAE was most often followed by myomectomy among those in their 30s, and by hysterectomy among those in their 50s. Younger women who initially had myomectomy were most likely to have repeat myomectomies over the 2 years of followup. After medical treatment, very few women in any age group had subsequent treatment within 2 years.

### **KQ2: Influence of Patient/Fibroid Characteristics on Effectiveness**

Among 97 randomized clinical trials of interventions, none were explicitly designed to address whether intervention effectiveness varied by patient or fibroid characteristics. Six studies provided some information about influence of characteristics on outcomes within or across arms (two of medications, two comparing UAE and surgery, one of myomectomy vs. no treatment, and one assessing the effects of baseline characteristics on outcomes among women who received high intensity focused ultrasound or radiofrequency ablation). None were statistically powered to examine effect modification by characteristics to answer questions such as: do those with fewer or smaller fibroids do better than those with more or larger fibroids? do women using hormonal contraceptive have different outcomes over time after this treatment compared to those who don't? and does baseline BMI determine results? As a result there is little data that can be used to guide care based on individual or fibroid characteristics.

### **KQ3: Risk of Leiomyosarcoma When Mass Thought to Be a Fibroid**

We replicated and updated the search from a recently published meta-analysis of prevalence of leiomyosarcoma among women treated for benign uterine fibroids.<sup>10</sup> We added 27 studies (26 cohort studies and 1 RCT) published since the conduct of the prior meta-analysis. We fit a

Bayesian binomial random effects model to update the estimate of prevalence of identifying a leiomyosarcoma at the time of surgery for presumed fibroids. The most inclusive estimated prevalence, from 68 prospective studies where conflicting data were clarified, is 0.02 percent (95% credible interval, 0.00 to 0.09%). When we limit the analysis to retrospective studies, the estimate is 0.09 percent (95% credible interval, 0.05 to 0.13%). Lack of precision means these estimates are not credibly different. In other words, using data from 160 studies, an unexpected leiomyosarcoma will be identified in fewer than one and up to 13 of every 10,000 surgeries performed for symptomatic fibroids.

#### **KQ4: Factors Affecting Leiomyosarcoma Survival**

Survival time for women with leiomyosarcoma for whom power morcellation was used was reduced compared with women for whom sharp morcellation (with a scalpel) was used and with those for whom the uterus was removed intact. From our meta-analysis, power morcellation has expected 5-year survival of 30 percent (95% Bayesian credible interval [BCI] 13% to 61%); scalpel morcellation, 59 percent (BCI: 33% to 84%); and intact removal, 60 percent (BCI: 24% to 98%). Though confidence bounds overlap, this analysis suggests method of morcellation may contribute to overall lethality of this aggressive form of cancer among those diagnosed with leiomyosarcoma after hysterectomy or myomectomy for fibroids. Evidence was insufficient to conclude whether patient and fibroid characteristics affected survival in women with leiomyosarcoma.

### **Discussion**

Evidence about effectiveness of treatment is synthesized across arms of studies that used the intervention in order to describe outcomes by intervention. If a study included different types of interventions, each is included in the related synthesis and discussion.

#### **KQ1. Effectiveness of Treatments for Fibroids**

Insufficient evidence suggests that expectant management results in minimal change over followup periods of a year

or less. Our findings are compatible with a prior review that included observational cohorts.<sup>12</sup> Outcomes are likely to differ by menopausal status, and longer term studies are needed.

Among medical therapies, GnRH agonists, mifepristone, and ulipristal reduced fibroid size and improved fibroid-related symptoms including bleeding and quality of life (moderate SOE, except for quality of life for GnRH agonist (low SOE)). Several other medications have promise but are not supported by sufficient evidence. Evidence is insufficient to detect differences by medication dose, duration of treatment, long term effectiveness and harms. Evidence is lacking for common clinical approaches such as non-steroidal anti-inflammatory drugs, oral contraceptives and is insufficient for the LNG-IUD.

With notable exceptions, the majority of surgical studies did not follow patients beyond the postoperative period. Therefore, many studies did not report patient-specific, or symptom related outcomes such as change in fibroid-related pain or bleeding. Many of the studies with surgical or procedural interventions reported intermediate outcomes only, such as technical success, hospital length of stay, or estimates of blood loss related to the surgery (e.g., postoperative hemoglobin, intra- or postoperative transfusion). Despite these limitations, we found that uterine artery embolization (UAE) (high SOE) as well as HIFU (low SOE) are effective for decreasing fibroid size/volume. Few other outcomes are well investigated for HIFU. UAE studies reported improved bleeding outcomes (high SOE), pain, and quality of life (moderate SOE). Myomectomy improves quality of life (low SOE). Hysterectomy improves quality of life (low SOE) and de facto resolves bleeding and bulk symptoms.

Table D summarizes the strength of evidence for the effectiveness of interventions on fibroid/uterine volume, fibroid-related bleeding, and quality of life because these were most frequently reported outcomes in the eligible studies for KQ1. For the complete assessment of strength of evidence, including risk of bias, study limitations, reporting bias, precision, consistency and directness of results, see the summaries presented in the full report.

**Table D. Strength of evidence and summary of findings for intervention effects on fibroid volume, fibroid-related bleeding, and quality of life**

<b>Intervention Category Total N Participants</b>	<b>Key Outcome(s)</b>	<b>Strength of Evidence</b>	<b>Key Findings</b>
Expectant management N=514	Change in fibroid size or uterine volume	Insufficient	Few women followed in 16 study arms; findings inconsistent; data inadequate to project course of watchful waiting (followup from 3-12 months)
	Change in bleeding	Insufficient	As above
	Quality of life	Insufficient	As above
GnRH agonist N=912	Change in fibroid size and uterine volume	Moderate	Consistent reductions in size or volume
	Change in bleeding	Moderate	Bleeding outcomes (e.g., menorrhagia, perceived blood loss, days of bleeding) consistently improved
	Quality of life	Low	Consistent improvements in arms reporting varied measures of quality of life
Mifepristone N=690	Change in fibroid size or uterine volume	Moderate	Consistent reductions in size or volume in study arms reporting these outcomes
	Change in bleeding	Moderate	Consistent improvements in bleeding outcomes (e.g., hemoglobin, amenorrhea, hypermenorrhea) in arms reporting these outcomes
	Quality of life	Moderate	Quality of life improved in study arms reporting varied measures of quality of life
Ulipristal N=1,095	Change in fibroid size and uterine volume	Moderate	Improvements in arms reporting these outcomes, with reductions generally maintained over 6 month followup
	Change in bleeding	Moderate	Bleeding outcomes (e.g., amenorrhea, hemoglobin) consistently improved in study arms reporting these outcomes
	Quality of life	Moderate	Improvement in fibroid-related quality of life in study arms reporting varied measures of quality of life
LNG-IUD N=30	Change in bleeding	Insufficient	Limited data in one small study with high risk of bias
Estrogen receptor agents (raloxifene, tamoxifen) N=117	Change in fibroid size and uterine volume	Low	Lack of effect on fibroid size with raloxifene
	Change in bleeding	Low	No changes in bleeding patterns or hemoglobin with raloxifene
Uterine artery embolization and occlusion N=1,376	Change in fibroid size and uterine volume with UAE	High	Consistent reduction in size in study arms reporting these outcomes, with two studies reporting continued effects for 5 years
	Change in bleeding with UAE	High	Improvements in bleeding outcomes (e.g., days of bleeding, hemoglobin, patient-rated bleeding) in study arms reporting these outcomes
	Quality of life with UAE	Moderate	Improvements in study arms reporting varied measures of quality of life
	Change in bleeding, fibroid size with uterine artery occlusion	Insufficient	Heterogeneity of intervention methods prohibits conclusions

<b>Intervention Category Total N Participants</b>	<b>Key Outcome(s)</b>	<b>Strength of Evidence</b>	<b>Key Findings</b>
HIFU for fibroid ablation N=264	Change in fibroid size and uterine volume	Low	Reduction in study arms reporting these outcomes
Radiofrequency fibroid ablation N =75	Change in bleeding	Insufficient	Limited data available to assess outcome
Endometrial ablation N=96	Change in bleeding	Insufficient	Limited data available to assess outcome
Myomectomy N=2,257	Change in fibroid size and uterine volume	N/A	N/A
	Change in bleeding	Insufficient	Few studies reported outcome; improvement in heavy bleeding noted in one study
	Quality of life	Low	Improvements in study arms reporting varied measures of quality of life
Hysterectomy N=1,116	Change in fibroid size and uterine volume	N/A	N/A
	Change in bleeding	N/A	N/A
	Quality of life	Low	Improvements in study arms reporting varied measures of quality of life

GnRH = gonadotropin-releasing hormone; HIFU = high intensity focused ultrasound; LNG-IUD = levonorgestrel intrauterine device; NA = not applicable, not measured; SOE = strength of evidence

### Comparative Effectiveness

Studies comparing different categories of intervention were rare. Most were single studies of the specific comparison investigated. Two studies compared UAE to myomectomy; 3 studies compared UAE to hysterectomy; and four studies compared different drugs, but because of quality and size of these single comparison studies, evidence is insufficient to guide choices between medications and procedures.

### Subsequent Intervention

For each of these interventions (uterine artery embolization, myomectomy, and medical management) and the subsequent treatment possibilities, the meta-analysis estimates 44 percent of women in their 30s received subsequent intervention after UAE. The findings are intriguing but inadequate to guide care about the sequence of treatments that may have the best outcomes because the overall quality of trials is limited and few women were followed long enough to identify treatment patterns. It is likely that much fewer than half of women will choose subsequent treatment in the near-term after an initial intervention. However, we can also speculate that the priorities which led women to participate in the

initial trials reflected the intensity of treatments they were most interested in pursuing so it is not surprising surgeries were most followed by other procedures promptly (within 6 months) by those were not satisfied with initial results while those who enrolled in medication trials were less likely to pursue more aggressive options. Because of the limited roster of studies that followed women for 6, 12, or 24 months, this analysis does not substitute for study of treatment trajectories in which all initial treatments can be followed by all possible combinations of next treatments.

### KQ2. Influence of Patient/Fibroid Characteristics on Effectiveness

Overall, data are inadequate to assist women in choosing one intervention over another based on her individual characteristics or the characteristics of her fibroids. Too few studies were adequately powered to determine within arms if one subgroup or another has superior outcomes within a treatment. Such information is required as a first step towards using individual characteristics to inform treatment choice.

### **KQ3. Risk of Leiomyosarcoma When Mass Thought To Be a Fibroid**

Overall, from 160 studies, we conclude that in every 10,000 who have surgery for fibroids, between 0 to 13 women, may be found to have a leiomyosarcoma. This is within the range of the point estimates that others have produced.<sup>10,24,25</sup> Our analysis includes a larger sample size, more prospective studies, and more recently published data. One advantage to prospective studies is that they employ standardized approaches for inclusion and data collection and apply quality controls for histopathology. Participants in prospective studies were somewhat younger than those in retrospective studies (mean age 38.5 versus 43.4 years, respectively). Among prospective studies 57 percent focused on myomectomy findings; 36 percent on hysterectomy, and 6 percent included both types of surgery. Among retrospective studies 32 percent focused on myomectomy; 49 percent hysterectomy, and 19 percent both. Because leiomyosarcoma risk increases with age<sup>25,26</sup>, differences in age distribution and potentially in surgery type would be expected to result in a lower prevalence estimated by our models.

The literature investigating the prevalence of leiomyosarcoma in presumed fibroids has grown rapidly and this continues to inform risk estimates. Unfortunately, the published literature does not contain enough detail to stratify risks by age, menopausal status, or surgical approach. Similarly, the literature lacks information on individual or fibroid characteristics that could discriminate those at high risk from those with lower risk. Thus the available data produces wide confidence intervals for broad groups of women when estimating rare outcomes. See “Limitations of the Evidence Base” in the full report for further discussion.

### **KQ4. Factors Affecting Leiomyosarcoma Survival**

At this time, definitive data that power morcellation is associated with poor long-term outcomes in the presence of unsuspected leiomyosarcoma is limited. In our meta-analysis of 24 studies that provide data about use of morcellation in three categories: none, scalpel, or power; we find that power morcellation may be a determinant of death from leiomyosarcoma. Some recent estimates in the literature find otherwise. As noted above, we cannot discern from the available literature any patient or fibroid characteristics that predict survival.

Uncertainty in estimates of prevalence and evolving data about methods for tissue extraction and their consequences

call for explorations of ethical and shared decision making topics to offer coherent care recommendations that support patients’ and surgeons’ autonomy.

### **Applicability**

Overall, our findings are widely applicable to the general population of women seeking treatment for uterine fibroids. For KQs 1 and 2 we set inclusion criteria for this review to women of any age with uterine fibroids with patient outcome data beyond intermediate outcomes only. We excluded studies in pregnant women, and restricted our synthesis to treatments currently available in the United States. Over 40 percent of the studies were conducted in European countries and another 27 percent were conducted in the United States or Canada. Although the outcomes collected may differ by country and by healthcare setting, the interventions were selected to be comparable so that the results reported in this review are expected to apply to women with fibroids in the United States.

Evaluation of expectant management was not an explicit aim of any trial. Sixteen studies with placebo arms or no treatment arms that included 514 women served as a surrogate. This population is not an ideal substitute as participants in the trials presumably hoped to receive active treatment and may report their status differently than women willing to be randomized to watchful waiting. This could restrict applicability but since the majority of studies included a plausible level of participant masking, they would be unlikely to know if they were on an active agent.

Medical management of fibroids was assessed in over 2,800 predominately premenopausal women from 43 studies (15 industry-sponsored and 11 conducted in the United States). Procedures, including UAE, HIFU, and radiofrequency fibroid ablation were evaluated in 28 studies including almost 2,000 women. Surgical studies evaluated hysterectomy, myomectomy, and endometrial ablation in over 3,000 women. Although none of the surgical studies were conducted in the United States, the surgical procedures are comparable to those widely available to women in the United States.

Data in these studies were inadequate to assess applicability based on patient characteristics (age, race/ethnicity, pregnancy intention, or menopausal status) or fibroid characteristics (size, position, and number) that could influence effectiveness outcomes.

While there are limitations in the literature as discussed below, the information that is available from these trials is relevant to contemporary practice. In summary, this

review is generally applicable to women in the United States seeking one of the many treatment choices currently available for fibroids.

For KQ3 and 4: Data can only be systematically obtained from published research or publically available research. Those represented in the literature may differ from the universe of women having surgery for fibroids in the US. The literature about risk and outcomes of leiomyosarcoma does not separate cases well by type or surgery or menopausal status. Prospective studies which include a greater representation of myomectomy patients may be more applicable for discussing risk among younger women.

### **Limitations of the Systematic Review Process**

Methodologic choices constrain the findings of this report. We chose to focus on publications in the English-language literature, to restrict to randomized clinical trials for the comparative effectiveness synthesis (KQs 1 and 2), and to review only those studies that included at least one intervention that is available in the United States. Similar reviews have documented in the past that language restrictions do not increase risk of omitting high quality trials. This is especially true for the topic of fibroids because the fibroid research community is small. Our technical expert panel and authors are familiar with prior and ongoing work and helped assure relevant studies have not been overlooked. Restricting to trials allowed us to sharply focus on proof of effectiveness. Because all individuals whose outcomes were assessed in these studies were randomly assigned to the intervention received, provider and patient biases in intervention choice are reduced and risk of confounding, difficult to fully assess or adjust for in cohort studies, is minimized. Random assignment to intervention arm in trials reduces bias and allows aggregation and summary of the findings by study arm, as presented in this report.

Restricting the review to randomized controlled trials limited ability to detect the full range of harms since studies were generally not designed or powered to evaluate harms, and many had a short duration of follow up.

Our analysis of subsequent intervention after a first intervention could be biased by the types of studies that reported this data and by differences in the willingness of women to be randomized to different types of intervention.

For meta-estimates related to leiomyosarcoma risk, available evidence based on pathology specimens for estimating presence of leiomyosarcoma in a mass

believed to be a fibroid is accruing rapidly and will likely continue after the production of this report. Our estimates and that of Pritts and colleagues<sup>10</sup> find that the estimates are lower in data from more contemporary prospective cohorts of women having surgery compared to retrospectively collected data. This may be explained by inaccuracies in retrospectively collected data even when pathology specimen banks are used to index a full population of surgical patients. On the other hand, it is important to note that prospectively collected data may enroll younger patients and a larger proportion undergoing myomectomies. As a rule, data for estimating rare events is volatile, which is demonstrated by the changes in prevalence estimates when we exclude studies that included hysteroscopy.

The risk of inaccuracy is especially true in understanding and estimating the degree to which morcellation method influences survival when a woman is found to have a leiomyosarcoma that was believed to be a fibroid. More nuanced data is needed to be able to include exact ages and uniform staging data at an individual level and to account for secular trends in aggressiveness of treatment and range of modalities used in treating leiomyosarcomas.

Focusing on interventions available in the United States, and excluding those that cannot be obtained here could neglect a promising intervention but does restrict the report to data that is of immediate value to women and their care providers who must make decisions among available options. We have included some interventions that are not widely available in the United States such as HIFU without MRI guidance. For any woman, her geographic location, local provider training or insurance coverage may restrict the availability of some options.

### **Limitations of the Evidence Base**

While the literature about the effectiveness of uterine fibroids treatment has grown since the last evidence report in 2007, significant gaps in knowledge persist. The 97 studies unique intervention arms enrolled 9,179 women, an average of 98 women per study with a range of 16 to 451. Individual studies were often small and powered to address a single continuous outcome such as hematocrit or score on a quality of life scale.

Our analytic framework was created by expert consensus to reflect the outcomes that matter to women when making decisions. The available literature has substantial gaps in collecting this information as indicated by the number of studies that addressed each of our eight primary outcomes. Fibroid characteristics and symptom status were the most

frequently reported outcomes, addressed in 65 percent and 59 percent of the studies respectively, though assessment techniques and measures varied. Other key outcomes including quality of life and satisfaction with outcomes (39%), sexual function (12%), and future reproductive outcomes (8%) were addressed in only a handful of studies. Detailed descriptions of subsequent treatment were reported in 29 percent of the included trials.

Little continuity exists in approaches to measuring outcomes and use of unvalidated measures is common. When data are combined across studies for a particular intervention, risk of serious rare harms cannot be fully assessed. In many instances ability to synthesize evidence across studies is absent, weak because of biased collection methods (e.g., assessors not blind to intervention), or difficult to aggregate across studies because of use of different metrics.

Paucity of “similar” articles (populations, settings, patient characteristics, and outcomes measured) also precludes efforts to pool data about characteristics of the study populations as they contribute to predicting outcomes. No studies were appropriately powered to understand whether specific groups of patients, such as those closer to menopause or with a specific symptom pattern have outcomes that are modified by those characteristics. Lastly, the lack of direct comparisons limits the information this can provide to help a woman or her care provider make an evidence-driven selection among choices in the context of the patient’s priorities.

Limitations about leiomyosarcoma data: Because cases are rare and detailed age data for non-cases is lacking, only rough models of risk by age can be produced.<sup>25</sup> We need more prospective studies that include nuanced data such as patient and fibroid characteristics, patient age, menopausal status and surgical approach, hormonal exposures and genetic factors so that we can give more accurate estimates to patients.

## Future Research

Key components of study design, analysis, and reporting remain the leading weaknesses of the literature for each topic addressed in this review. Overall, the literature identified is limited by the following gaps and problems discussed in detail in the full report. Future research should aim to remediate these concerns:

- Ability to assess internal and external validity
- Study populations of adequate size for assessing key outcomes

- Use of standard nomenclature and validated measures
- Analysis methods matched to the outcomes of interest
- Direct comparisons of treatment options
- Formal development of patient centered outcome measures for fibroid care

A range of content priorities also need to be addressed. These include the burden of disease and societal costs from loss of ability to function well in the usual family or occupational roles. Transitions associated with appearance of uterine fibroids, growth patterns, and influences on growth (e.g., concurrent medical conditions like diabetes, use of medications like hormonal contraception, influence of lactation and duration) are high-priority topics, as are predictors of symptom development and resolution. Variation in care-seeking behaviors, differences in severity at presentation, and health and quality of life outcomes are other matters that investigators should attempt to address. Likewise reproductive outcomes such as fertility and risk of future pregnancy complications are very important to women as they make decisions about fibroid treatment and the current literature is insufficient to guide choices. In addition, the current literature cannot address from trials whether disparities between white and black women in the age at appearance of fibroids and in the number and size of fibroids also foreshadows different treatment outcomes and durability of results.

In current practice, women without symptoms may forego intervention because of the general belief that care should be aimed at improving symptoms or addressing a specific clinical concern such as difficulty conceiving or recurrent pregnancy loss. Although foregoing intervention can be wise in the absence of data that the intervention will prevent future difficulties, research on the natural history of fibroids and likelihood of developing symptoms or other health effects is limited. No data is available to indicate whether use of therapeutics short of surgery might forestall or prevent future changes in fibroids or appearance of symptoms. The concept of preventive strategies is appealing. However, as long as the etiology of fibroids remains unclear, preliminary trials are not assessing lifestyle interventions, and the prospect for dietary management, nutritional supplementation, exercise, hormonal management, or other prevention trials is slim.

The clinical research agenda will likely depend on new translational research and large-scale epidemiology studies. Much remains to be learned that will require large-scale prospective observational studies of sufficient size

and rigor to support time-to-event analysis of outcomes, such as that being conducted in the COMPARE Uterine Fibroids 10,000 woman registry supported by AHRQ and PCORI. These studies may afford greater power to examine effect modification and to determine trajectories of care over a reproductive lifespan for women with fibroids. Additionally, such studies will be better able to estimate both common and rare harms, including the risk of occult leiomyosarcoma. Research effort must be focused on documenting first the course and consequences of uterine fibroids using optimal imaging strategies. We must then deploy more robust statistical techniques across aggregated data in order to understand the modifiers of that course and of the effectiveness of treatment, so that we can offer women an accurate account of the likely outcome of intervention choices based on their individual status.

## Conclusions

A range of interventions are effective for reducing fibroid size and improving symptoms. Some medications and procedures also improve quality of life. Direct comparisons among treatment options remain sparse. No studies have explicitly evaluated expectant management, which is a crucial missing piece of the evidence about whether symptoms relapse and remit. The literature must come to include uniformly longer followup to determine whether women's objectives for treatment were met by the intervention received. Few women have only one concern driving their desire for intervention, yet remarkably many trials are directed at evaluating a single outcome. Likewise concerns about harms, such as drug side effects, serious surgical complications, and risk of undetected leiomyosarcoma, need to exploit larger and more nuanced data to be able to better determine what individual and fibroid characteristics best predict adverse events to better inform personalized care.

Across management options, we must note that lack of evidence is not equivalent to evidence of no benefit or of harm. Evidence to inform probability of risk or benefit based on patient characteristics is lacking. Uncontrolled studies are not a substitute since they are notably biased for overestimating the degree of benefit subsequently reported in randomized trials. Indeed, not uncommonly, trials negate the findings of what in this case is largely retrospective and case series research. The current state of the literature does not permit definitive conclusions about comparative benefit, harm, or relative costs to achieve similar results across the range of available options and lacks strength of evidence for interventions such as use of continuous birth

control pill regimens, progesterone containing IUDs, and endometrial ablation that are often used in routine clinical practice.

Given how common and concerning fibroids can be to women and their care providers, a redoubled emphasis on promoting high-quality fibroid research in the United States is imperative. Women need better information to guide their choices.

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## Full Report

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