

# Abnormal Uterine Bleeding and Uterine Fibroids (for Kentucky Only)

Policy Number: CS002KY.02  
Effective Date: July 1, 2021

[Instructions for Use](#)

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Related Policy
<ul style="list-style-type: none"> <li><a href="#">Hysterectomy</a></li> </ul>

## Application

This Medical Policy only applies to the state of Kentucky.

## Coverage Rationale

### Levonorgestrel-Releasing Intrauterine Device

Levonorgestrel-releasing intrauterine devices (LNG-IUD) (e.g., Mirena®, Skyla®, Liletta® or Kyleena™) are proven and medically necessary for treating menorrhagia. Refer to the [U.S. Food and Drug Administration \(FDA\)](#) section for additional information.

### Uterine Fibroids

Uterine artery embolization (UAE) is proven and medically necessary for treating symptomatic uterine fibroids when there is documentation of evaluation of abnormal uterine bleeding (AUB) including endometrial biopsy for individuals > 40 years of age and a pap smear screening consistent with current guidelines. For medical necessity clinical coverage criteria, refer to the InterQual® 2021, Apr. 2021 Release, CP: Procedures, Uterine Artery Embolization (UAE).

Click [here](#) to view the InterQual® criteria.

UAE is unproven and not medically necessary for the purpose of preserving childbearing potential for women with symptomatic uterine fibroids due to insufficient evidence of efficacy.

The following procedures are unproven and not medically necessary for treating uterine fibroids due to insufficient evidence of efficacy:

- Magnetic resonance-guided focused ultrasound ablation (MRgFUS)
- Ultrasound-guided radiofrequency ablation (e.g., Acessa™, Sonata®)

## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
<b>Uterine Fibroids</b>	
0071T	Focused ultrasound ablation of uterine leiomyomata, including MR guidance; total leiomyomata volume less than 200 cc of tissue
0072T	Focused ultrasound ablation of uterine leiomyomata, including MR guidance; total leiomyomata volume greater or equal to 200 cc of tissue
0404T	Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency
37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
58578	Unlisted laparoscopy procedure, uterus
58674	Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency
58999	Unlisted procedure, female genital system (nonobstetrical)

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HCPCS Code	Description
<b>Levonorgestrel-Releasing Intrauterine Device</b>	
J7296	Levonorgestrel-releasing intrauterine contraceptive system, (Kyleena), 19.5 mg
J7297	Levonorgestrel-releasing intrauterine contraceptive system (Liletta), 52 mg
J7298	Levonorgestrel-releasing intrauterine contraceptive system (Mirena), 52 mg
J7301	Levonorgestrel-releasing intrauterine contraceptive system (Skyla), 13.5 mg
J7306	Levonorgestrel (contraceptive) implant system, including implants and supplies
S4981	Insertion of levonorgestrel-releasing intrauterine system

## Description of Services

Abnormal uterine bleeding (AUB) in women of childbearing age is defined as any change in menstrual period frequency or duration, a change in amount of flow or any bleeding between cycles. In postmenopausal women, AUB includes vaginal bleeding 12 months or more after the cessation of menstruation, or unpredictable bleeding in patients who have been receiving hormone therapy for 12 months or more. AUB terms include oligomenorrhea (bleeding occurs at intervals of more than 35 days), polymenorrhea (bleeding occurs at intervals of less than 21 days), menorrhagia (bleeding occurs at normal intervals but with heavy flow or duration of more than 7 days), menometrorrhagia (bleeding occurs at irregular, noncyclic intervals and with heavy flow or duration more than 7 days) and metrorrhagia (irregular bleeding occurs between ovulatory cycles). Menorrhagia can be idiopathic or can be associated with underlying uterine lesions such as fibroids or polyps, pelvic pathology, anatomical abnormalities, systemic illness, hormonal imbalance or certain medications. Idiopathic menorrhagia that is not related to a specific underlying condition is called AUB. All these conditions associated with menorrhagia can be referred to as AUB, although it is also possible to have some conditions such as fibroids or an anatomical abnormality with normal menses. The focus in this policy is on treatment options when the bleeding pattern is abnormal.

Conservative management of AUB includes watchful waiting and pharmacological therapy. Hormone therapy may cause the fibroids to shrink; however, they will quickly return to their original mass once therapy has been discontinued. Another

treatment option is dilation and curettage. Hysterectomy is available when symptoms cannot be controlled by conservative treatment.

According to ACOG, fibroids occur in approximately 25-50% of all women, most commonly in those ages 30-40 years. Uterine fibroids (also known as leiomyomata) are benign tumors of the uterus. They have a rich blood supply and may cause excessive uterine bleeding, uterine enlargement and mass or bulk related symptoms such as pelvic pain and pressure, urinary frequency and abdominal distension. Uterine fibroid embolization (UFE) is indicated for individuals with clinically documented fibroids and fibroid-related symptoms and a viable alternative to hysterectomy surgery. Recommendations prior to UFE treatment include an endometrial biopsy to rule out malignancy or hyperplasia (Bradley 2018). Alternate minimally invasive procedures such as UFE are performed in an outpatient setting resulting in shorter recovery times, less complications and elimination of overnight hospital stays.

### **Levonorgestrel-Releasing Intrauterine Device (LNG-IUD)**

The local administration of the progestin levonorgestrel is delivered via an intrauterine device (IUD). The local delivery of this hormone causes the endometrium to become insensitive to ovarian estradiol leading to atrophy of the endometrial glands, inactivation of the endometrial epithelium and suppression of endometrial growth and activity.

### **Uterine Artery Embolization (UAE)**

This procedure injects particles via the uterine arteries to block blood supply to uterine fibroids, causing them to shrink.

### **Magnetic Resonance-Guided Focused Ultrasound (MRgFUS)**

This procedure combines real-time MR-guidance with high-intensity focused ultrasound for the noninvasive thermal ablation of uterine fibroids. Tumor ablation is performed by focusing a collection of ultrasonic beams to increase sonic beam intensity at a point deep within the tissue to cause thermal coagulation while sparing normal tissues.

### **Ultrasound-Guided Radiofrequency Ablation**

- Laparoscopic Ultrasound-Guided Radiofrequency Ablation: This minimally invasive procedure uses a laparoscopic ultrasound probe to determine the location and size of fibroids. Then a small electrode array delivers radiofrequency energy to destroy the fibroids.
- Transcervical Ultrasound-Guided Radiofrequency Ablation: This minimally invasive procedure destroys fibroids using a transcervical radiofrequency ablation device under integrated, real-time, intrauterine ultrasound imaging guidance.

## **Clinical Evidence**

### **Levonorgestrel-Releasing Intrauterine Device (LNG-IUD)**

Cim et al. (2018) reported two-year follow-up data of patients with abnormal uterine bleeding (AUB) after insertion of the levonorgestrel-releasing intrauterine system (LNG-IUS). One hundred and six parous women aged 33-48 years with recurrent heavy menstrual bleeding (HMB) participated in this study, and were followed for 1, 3, 6, 12, 18, and 24 months following the insertion. The authors reported that the LNG-IUS was well tolerated by all women. Pre-treatment of the use of the LNG-IUS, endometrial biopsy patterns for irregular proliferative endometrium and for atypical simple hyperplasia were 34/106 (32.08%) and 61/106 (57.55%) respectively and after treatment no abnormal pathologic findings were determined ( $p < 0.001$ ).

Louie et al. (2017) evaluated comparative clinical outcomes after placement of LNG-IUS, ablation, or hysterectomy for AUB. A decision tree was generated to compare clinical outcomes in a hypothetical cohort of 100,000 premenopausal women with nonmalignant AUB. Complications, mortality, and treatment outcomes were evaluated over a 5-year period, with calculated cumulative quality-adjusted life years (QALYs), and probabilistic sensitivity analysis. The LNG-IUS had the highest number of QALYs (406, 920), followed by hysterectomy (403, 466), non-resectoscopic ablation (399, 244), and resectoscopic ablation (395, 827). Ablation had more treatment failures and complications than LNG-IUS and hysterectomy. According to the authors, findings were robust in sensitivity analysis.

A Cochrane review (Marjoribanks et al., 2016) compared the effectiveness, safety and acceptability of surgery versus medical therapy for heavy menstrual bleeding. Fifteen randomized controlled trials (n=1289) comparing surgery versus oral medication or LNG-IUD for treating heavy menstrual bleeding were included. The authors concluded that hysterectomy, endometrial

surgery and the LNG-IUD were all effective in reducing heavy menstrual bleeding, though surgery was most effective, at least over the short term. These treatments suited most women better than oral medication. Although hysterectomy will stop heavy menstrual bleeding, it is associated with serious complications. Both conservative surgery and LNG-IUD appear to be safe, acceptable and effective.

An updated Cochrane systematic review by Lethaby et al. (2015) evaluated the safety and efficacy of the LNG-IUD for heavy menstrual bleeding (HMB). Twenty-one randomized controlled trials in women of reproductive age treated with progesterone or progestogen-releasing intrauterine devices versus no treatment, placebo or other medical or surgical therapy for heavy menstrual bleeding were included. The authors concluded that the LNG-IUD is more effective than oral medication as a treatment for HMB. The device is associated with a greater reduction in HMB, improved quality of life and appears to be more acceptable long term but is associated with more minor adverse effects than oral therapy. When compared to endometrial ablation, it is not clear whether the LNG-IUD offers any benefits with regard to reduced HMB, and satisfaction rates and quality of life measures were similar. Limitations included inconsistency and inadequate reporting of study methods.

In a systematic review of twenty-six studies, Matteson et al. (2013) compared the effectiveness of nonsurgical abnormal uterine bleeding treatments for bleeding control, quality of life (QOL), pain, sexual health, patient satisfaction, additional treatments needed and adverse events. Interventions included the levonorgestrel intrauterine system, combined oral contraceptive pills (OCPs), progestins, nonsteroidal anti-inflammatory drugs (NSAIDs) and antifibrinolytics. For reduction of menstrual bleeding in women with abnormal uterine bleeding presumed secondary to endometrial dysfunction, the levonorgestrel intrauterine system (71-95% reduction), combined OCPs (35-69% reduction), extended cycle oral progestins (87% reduction), tranexamic acid (26-54% reduction) and NSAIDs (10-52% reduction) were all effective treatments. The levonorgestrel intrauterine system, combined OCPs and antifibrinolytics were all superior to luteal-phase progestins (20% increase in bleeding to 67% reduction). The levonorgestrel intrauterine system was superior to combined OCPs and NSAIDs. Antifibrinolytics were superior to NSAIDs for menstrual bleeding reduction. Data were limited on other important outcomes such as QOL for women with abnormal uterine bleeding presumed secondary to endometrial dysfunction and for all outcomes for women with abnormal uterine bleeding presumed secondary to ovulatory dysfunction.

In another systematic review, Matteson et al. (2012) compared hysterectomy with less-invasive alternatives for abnormal uterine bleeding (AUB). Nine randomized controlled trials comparing bleeding, quality of life, pain, sexual health, satisfaction, need for subsequent surgery and adverse events were included. Endometrial ablation, levonorgestrel intrauterine system and medications were associated with lower risk of adverse events but higher risk of additional treatments than hysterectomy. Compared to ablation, hysterectomy had superior long-term pain and bleeding control. Compared with the levonorgestrel intrauterine system, hysterectomy had superior control of bleeding. No other differences between treatments were found. The review group concluded that less-invasive treatment options for AUB result in improvement in quality of life but carry significant risk of retreatment caused by unsatisfactory results. Although hysterectomy is the most effective treatment for AUB, it carries the highest risk for adverse events.

Kaunitz et al. (2010) compared the efficacy and safety of the levonorgestrel-releasing intrauterine system and oral medroxyprogesterone acetate in the treatment of idiopathic heavy menstrual bleeding. In this multicenter, randomized, controlled study, women aged 18 years or older with heavy menstrual bleeding (menstrual blood loss 80 mL or more per cycle) were randomly assigned to six cycles of treatment with either levonorgestrel-releasing intrauterine system or oral medroxyprogesterone acetate. Of 807 women screened, 165 were randomly assigned to treatment (levonorgestrel-releasing intrauterine system n=82, oral medroxyprogesterone acetate n=83). At the end of the study, the absolute reduction in median menstrual blood loss was significantly greater in the levonorgestrel-releasing intrauterine system group than in the medroxyprogesterone acetate arm, and the proportion of women with successful treatment was significantly higher for the levonorgestrel-releasing intrauterine system (84.8%) than for medroxyprogesterone acetate (22.2%).

Kaunitz et al. (2009) compared the effects of the levonorgestrel intrauterine system and endometrial ablation in reducing heavy menstrual bleeding. The systematic review and meta-analysis were restricted to randomized controlled trials in which menstrual blood loss was reported using pictorial blood loss assessment chart scores. Six randomized controlled trials that included 390 women (levonorgestrel intrauterine system, n=196; endometrial ablation, n=194) were reviewed. Three studies pertained to first-generation endometrial ablation (manual hysteroscopy) and three to second-generation endometrial ablation (thermal balloon). Both treatment modalities were associated with similar reductions in menstrual blood loss after 6 months, 12 months and 24 months. In addition, both treatments were generally associated with similar improvements in quality of life in five studies that reported this as an outcome. No major complications occurred with either treatment modality in these small trials. The authors

concluded that the efficacy of the levonorgestrel intrauterine system in the management of heavy menstrual bleeding appears to have similar therapeutic effects to that of endometrial ablation up to 2 years after treatment.

A National Institute of Health and Care Excellence (NICE) guideline on assessment and management of heavy menstrual bleeding recommends LNG-IUS as the first treatment for women with no identified pathology, fibroids less than 3 cm in diameter, or suspected or diagnosed adenomyosis. If the treatment is unsuccessful, the patient declines pharmacological treatment, or symptoms are severe, referral to a specialist is recommended to discuss additional options. For women with fibroids greater than 3 cm in diameter, LNG-IUS is listed as a pharmacologic option. (NICE, 2020)

## Uterine Artery Embolization (UAE)

Manyonda et al. (2020) conducted a multicenter, randomized, open-label trial which compared myomectomy and uterine artery embolization in women with symptomatic uterine fibroids. 254 women were recruited out of a potential 650 and randomly assigned in a 1:1 ratio to undergo a myomectomy or uterine artery embolization. Myomectomy was performed by the route preferred by the operating gynecologist (e.g., open abdominal, hysteroscopic, laparoscopic, or a combination of these). Embolization of the uterine arteries was performed under fluoroscopic guidance and the specific embolic agent used was at the discretion of the interventional radiologist. The tool used for primary outcome was the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire; scores ranged from 0 to 100 with higher scores indicating a better quality of life. Primary and secondary outcome data was collected from each participant at 6 months, 1 year, and 2 years after randomization. The authors found the mean scores on UFS-QOL at two years were substantially higher in both groups, but the magnitude of improvement was greater in the myomectomy group. At 2 years, 93% of the women in the myomectomy group would recommend the procedure to a friend versus only 84% in the embolization group would make their procedure recommendation. Complications associated with both procedures were low. Limitations included loss to followup, lack of blinding, a substantial amount of missing data on the FSH and luteinizing hormone levels due to lack of collection of blood samples, a number of participants did not receive the intervention to which they had been assigned despite randomization and many women declined to participate in the trial due to wanting a specific treatment option. The authors concluded this multicenter trial showed the superiority of myomectomy over uterine artery embolization with respect to health-related quality of life.

Karlsen et al. (2018) conducted a systematic review of the reported rates of pregnancy and miscarriage after treatment of uterine fibroids with UAE. Randomized controlled trials (RCT), controlled clinical trials, comparative before-after trials, cohort studies, case-control studies and case series where UAE treatment of premenopausal women was performed for uterine fibroids with and where a control intervention was included. The PRISMA guideline was used to do a systematic review using the main outcomes pregnancy rate and miscarriage rate. Risk of bias was assessed by the Cochrane risk of bias tool or by ROBINS-I. The quality of evidence was assessed by the GRADE approach. 17 studies comprising 989 patients were selected and included 1 RCT, 2 cohort studies, and 14 case series. The results showed pregnancy rates after UAE were 50% in the RCT and 51 and 69% in the cohort studies. Among the case series median pregnancy rate was 29%. Miscarriage rates were 64% in the RCT. Miscarriage rates at 56 and 34% were found in the cohort studies after UAE. The median miscarriage rate was 25% in the case series. The authors concluded that pregnancy rate was found to be lower and miscarriage rate higher after UAE than after myomectomy. However, they found very low quality of evidence regarding the assessed outcomes and the reported proportions are uncertain. There is a need for improved prospective randomized studies to improve the evidence base.

Torre et al. (2017) conducted a non-comparative open-label trial, on 15 women  $\leq 40$  years, presenting with multiple symptomatic fibroids (at least 3,  $\geq 3$  cm), immediate pregnancy wish, and no associated infertility factor. Patients were eligible for surgical multiple myomectomy, but carefully elected uterine artery embolization (UAE). During the year following UAE, 9 patients actively wishing to conceive delivered 5 live births. Women were followed for 43.1 months (95%CI 32.4-53.9); 10 live births occurred in 8 patients, and 5 patients required secondary surgeries for fibroids. Although in this study women without associated infertility factors demonstrated an encouraging capacity to deliver after UAE, randomized controlled trials comparing UAE and myomectomy are warranted.

Pisco et al. (2017) conducted a retrospective analysis of prospectively collected data of 359 women with uterine fibroids and/or adenomyosis who were unable to conceive. The purpose of the study was to determine pregnancy rates after conventional and partial uterine fibroid embolization (UFE). The mean follow-up period was 69 months. During follow-up, 149 women became pregnant, 131 women had live births, and 16 women had several pregnancies, resulting in a total of 150 live newborns. It was the first pregnancy for 85.5% (112 of 131) of women. Spontaneous pregnancy rates at 1 year and 2 years after UFE were 29.5% and 40.1%. A dominant submucosal fibroid and ischemia greater than or equal to 90% had greater likelihood of spontaneous pregnancy. Complication rates in patients treated with partial UFE (14.6%) were not greater than rates in patients treated with

conventional UFE (23.1%, P = .04). The authors concluded that partial UFE may be safe and effective outpatient procedures for women with uterine fibroids who want to conceive. Limitations included the study was performed at a single center along with a nonstandardized technique utilized by the radiologists; additional randomized controlled trials comparing UFE to myomectomy are needed.

Szkodziak et al. (2017) evaluated minimally invasive procedures in the management of uterine fibroids through a systematic review. They reported that the clinical efficacy index for uterine artery embolization (UAE) in the treatment of excessive menstrual bleeding, pelvic pain and pressure symptoms associated with tumor mass are located in the following ranges: 81-96%, 70-100% and 46-100%. A 25-60% reduction in uterine volume has been observed within 3 to 6 months after the procedure. In a long-term (up to 5 years) follow-up after UAE, in over 70% of patients there was a significant improvement in the quality of life, while 16-23% of the patients required another intervention. Potential complications include infection, expulsion of demarcated, necrotic pieces of fibroids through the cervical canal, and nontarget embolization of other pelvic organs. After UAE, a significant shortening and decrease of the amount of menstrual bleeding can be observed, which is considered by the authors to be a beneficial effect of this procedure. However, the total lack of menstruation in many studies is given as the effect of post-embolization ovarian failure.

Fonseca et al. (2017) conducted a meta-analysis and indirect treatment comparison to examine the comparative efficacy and safety of surgical procedures to treat symptomatic uterine leiomyomas compared with UAE. Data from 986 patients submitted to UAE (n = 527) or surgery (n = 459) were analyzed. UAE had a lower risk of major complications and a higher risk of minor complications; UAE had a higher risk of re-intervention up to 2 years and up to 5 years; UAE had a similar risk of follicle-stimulating hormone levels >40 IU/L after 6 months and of recommending the procedure to another patient up to 5 years after treatment. Compared with surgery, UAE had lower rates of major complications with an increased risk of re-intervention up to 2 and 5 years after the first procedure. Surgery had a similar risk of ovarian failure and similar recommendation of the procedure to another patient. However, the number of trials was limited, and there was a high risk of bias in at least 2 domains, and non-blinding of study participants and staff occurred.

Havryliuk et al. (2017) conducted a systematic review and meta-analysis from clinical studies that described populations of premenopausal women seeking surgical management (both uterine-sparing and hysterectomy) for their symptomatic fibroids. Procedures included in the analysis were myomectomy, UAE, Lap-RFA, MRg-FUS, and hysterectomy. For UAE (N=1154), the mean follow-up period was 13.5 months, overall complication rate 16.8% (2.7% major, 14.0% minor), and reintervention rate 14.8%. Patients reported, however, greater improvement of their fibroid symptoms as reflected by post-treatment high HRQL and EQ-5D scores and low symptom severity scores. Patients who underwent UAE had the largest fibroid diameters compared to all other treatment groups and the largest proportion of intramural myomas; these factors may have contributed to the observed outcomes. The chance of developing premature ovarian failure was very low in patients who were younger than 40 years of age; however, this risk increased in women older than 45 years. The authors state that limitations of this review include the inherent heterogeneity among studies; only a portion of the included studies were randomized controlled trials, most were not and were assigned an ACOG quality score of B; and lack of uniformity in reporting conventions. Further comprehensive prospective research, ideally in the form of well-powered randomized controlled trials, is needed to validate the specific treatment modality preferred for specific anatomical variances of fibroids.

Torre et al. (2014) conducted a prospective cohort study of 66 consecutive patients with extensive symptomatic fibroids who desired a future pregnancy and were treated with UAE. Patients were not eligible for abdominal myomectomy because of fibroid recurrence despite previous surgery, because of current risks of surgery, or because of patient refusal. Ovarian reserve demonstrated no change after embolization. Women were followed for  $33.4 \pm 14.5$  months; only 1 in 31 women who were actively attempting to conceive became pregnant which ended in miscarriage. The authors concluded that the low reproductive outcomes reported in the study suggest that UAE should not be performed routinely in young women of childbearing age with extensive fibroids. Although this finding was established in a population for whom abdominal myomectomy was declined, a possible adverse effect of UAE on fertility potential should be considered for woman of childbearing age scheduled for embolization. Limitations included lack of control group and smaller sample size.

Panagiotopoulou et al. (2014) evaluated the effectiveness of uterine-sparing interventions for women with symptomatic uterine fibroids who wish to preserve their uterus. Five trials, involving 436 women were included. Two compared uterine artery embolization with myomectomy and three compared uterine artery embolization with laparoscopic uterine artery occlusion. Indirect treatment comparison showed that myomectomy and uterine artery embolization resulted in higher rates of patient satisfaction and lower rates of clinical failure than laparoscopic uterine artery occlusion. Myomectomy resulted in a lower

reintervention rate than uterine artery embolization and laparoscopic uterine artery occlusion even though the latter techniques had an advantage over myomectomy because of shorter hospitalization and quicker recovery. There was no evidence of difference between the three techniques in ovarian failure and complications rates. The evidence for reproductive outcomes is poor. The authors concluded that these results suggest that laparoscopic uterine artery occlusion is less effective than uterine artery embolization and myomectomy in treatment of symptomatic fibroids. The choice between uterine artery embolization and myomectomy should be based on individuals' expectations and fully informed discussion. Limitations of the study included the relatively low number of included studies and low number of participants; further RCTs providing longer follow up and assessing the safety and efficacy of the interventions are warranted.

Martin et al. (2013) performed a systematic review of complications and reinterventions in uterine artery embolization (UAE) for symptomatic uterine fibroids. In randomized clinical trials, common complications were discharge and fever (4%), bilateral uterine artery embolization (UAE) failure (4%) and postembolization syndrome (2.86%). Two trials showed a significantly decreased risk in major complications with UAE. None of the trials showed a significant difference in minor complications of UAE. None of the trials showed a significant difference in risk for overall complications of UAE. Three trials showed a significantly increased risk for reintervention with UAE. In 76 nonrandomized studies, common complications were amenorrhea (4.26%), pain (3.59%) and discharge and fever (3.37%). In 41 case studies, common complications were discharge and fever (n=22 cases), repeat UAE (n=6 cases) and fibroid expulsion (n=5 cases). The authors concluded that, overall, UAE has a significantly lower rate of major complications relative to surgery, but it comes at the cost of increased risk of reintervention.

Toor et al. (2012) performed a systematic review and meta-analysis to determine complication rates and effectiveness of uterine artery embolization (UAE) in the treatment of symptomatic uterine fibroids. Fifty-four studies met the inclusion criteria (n=8159). There were no reported deaths. Major complications occurred at a rate of 2.9%. The rate of hysterectomy for resolution of a complication from UAE was 0.7% (0.5-0.9%) and the rate of readmission was 2.7% (1.9-3.7%). Other complications recorded were leiomyoma tissue passage (4.7% [3.9-5.7%]), deep venous thrombosis or pulmonary embolism (0.2% [0.2-0.4%]) and permanent amenorrhea (3.9% [2.7-5.3%]). Reintervention rates including repeat UAE, myomectomy, or hysterectomy calculated per patient-year occurred at 5.3% (4.2-6.4%) with follow-up ranging from 0.25 to 5 years. Clinical symptomatic improvement ranged from 78% to 90%, with follow-up ranging from 0.25 to 2 years. The authors concluded that symptomatic uterine leiomyoma treatment by UAE is an effective procedure with a low rate of major complications supporting its use as an alternative to hysterectomy. Limitations include only using English language articles which may have missed other valid studies and underestimation of complications due to variable follow up durations between studies.

In an updated Cochrane systematic review, Gupta et al. (2014) assessed the benefits and risks of UAE versus other medical or surgical interventions for symptomatic uterine fibroids. The primary outcomes of the review were patient satisfaction and live birth rate (among women seeking live birth). Seven randomized controlled trials (n=793) were included in this review. Three trials compared UAE with abdominal hysterectomy, two trials compared UAE with myomectomy and two trials compared UAE with either type of surgery (53 hysterectomies and 62 myomectomies). The authors reported no evidence of a difference in patient satisfaction rates at up to two years following UAE versus surgery (myomectomy or hysterectomy). Findings at five-year follow-up were similarly inconclusive. There was very low-quality evidence to suggest that myomectomy may be associated with better fertility outcomes than UAE, but this information was only available from a selected subgroup in one small trial. The authors found no clear evidence of a difference between UAE and surgery in the risk of major complications, but UAE was associated with a higher rate of minor complications and an increased likelihood of requiring surgical intervention within two to five years of the initial procedure. Limitations included wide range in the quality of evidence, failure to clearly report methods and lack of blinding for subjective outcomes.

Jun et al. (2012) compared the efficacy and safety of uterine artery embolization (UAE) for symptomatic uterine fibroids with surgery. Patients were randomly assigned to undergo either UAE (n=63) or surgery (n=64). A meta-analysis of existing studies was also performed. There were significant improvements in UAE groups in most components of quality of life assessment at 6 months. The UAE group had a shorter hospital stay and a shorter recovery time compared with the surgical group. During the follow-up, there were no differences in complications incidence, but the UAE group had less major complications. A meta-analysis of this and existing studies further suggested that the UAE group had a shorter hospital stay, a shorter recovery time and less major complications than the surgical group. The authors concluded that more studies are needed to evaluate the long-term effects and impact of UAE on fertility.

In a retrospective analysis, Pisco et al. (2011) evaluated the outcome of pregnancy after UAE in 74 patients who wanted to conceive. The length of the follow-up period was 4.5 years; however, all the pregnancies occurred between 4 and 22 months

after UFE. Of the study participants, 44 became pregnant (59.5%). There are five (11.3%) ongoing pregnancies and 39 (88.7%) finished pregnancies, with 33 successful live births (84.6%), four spontaneous abortions (10.3%), one induced abortion, and one stillbirth. There were 22 cesarean deliveries (66.6%), two preterm deliveries at 36 weeks (6.1%), and five low birth weights. Although the authors concluded that UFE appears to be safe, study limitations include non-randomization in comparison with myomectomy, and small patient population.

In a systematic review and meta-analysis, van der Kooij et al. (2011) analyzed the evidence on short-, mid- and long-term results of uterine artery embolization (UAE) compared to surgery (hysterectomy/myomectomy) in premenopausal women with heavy menstrual bleeding caused by symptomatic uterine fibroids. Four randomized controlled trials with a total of 515 patients were included. Short-term advantages of uterine artery embolization over surgery included less blood loss, shorter hospital stays and quicker return to usual activities. Mid- and long-term results showed comparable health-related quality of life results and a higher reintervention rate in the uterine artery embolization group.

In a multicenter, randomized trial, Moss et al. (2011) compared the long-term results of uterine artery embolization (UAE) with surgery for women with symptomatic uterine fibroids. A total of 157 women were randomized (in a 2:1 ratio) to UAE (n=106) and surgery (hysterectomy n=42; myomectomy n=9). There were no significant differences between groups regarding quality of life at 5 years. Rates of adverse events were similar in both groups. The 5-year intervention rate for treatment failure or complications was 32% in the UAE arm and 4% in the surgery arm. The authors concluded that UAE is a satisfactory alternative to surgery for fibroids. The less invasive nature of UAE needs to be balanced against the need for re-intervention in almost a third of patients.

In a systematic review prepared for the Agency for Healthcare Research and Quality (AHRQ), Hartmann et al. (2017) summarized that 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. They noted that the effect of UAE on reproductive outcomes is not well studied and evidence is insufficient to guide care or determine safety.

A National Institute for Health and Care Excellence (NICE) guidance document states that current evidence on uterine artery embolization (UAE) for fibroids shows that the procedure is efficacious for symptom relief in the short and medium term for a substantial proportion of patients. There are no major safety concerns. Therefore, this procedure may be used provided that normal arrangements are in place for clinical governance and audit (NICE, 2010).

The NICE guideline on the management of heavy menstrual bleeding (2020) lists UAE as an option for women with fibroids 3 cm or more in diameter. They recommend that the woman's uterus and fibroid(s) be assessed by ultrasound prior to the procedure, and if further information about fibroid position, size, number and vascularity is needed, MRI should be considered.

van der Kooij et al. (2010) compared clinical outcomes and health related quality of life (HRQOL) 5 years after uterine artery embolization (UAE) or hysterectomy in the treatment of menorrhagia caused by uterine fibroids. Patients with symptomatic uterine fibroids who were eligible for hysterectomy were assigned randomly 1:1 to hysterectomy (n=89) or UAE (n=88). Endpoints after 5 years were reintervention rates, menorrhagia and HRQOL measures that were assessed by validated questionnaires. Five years after treatment 23 of 81 UAE patients (28.4%) had undergone a hysterectomy because of insufficient improvement of complaints (24.7% after successful UAE). HRQOL measures improved significantly and remained stable until the 5-year follow-up evaluation, with no differences between the groups. UAE had a positive effect both on urinary and defecation function. de Bruijn et al. (2016) reported outcomes at 10 years. Ten years after treatment, 28 of 81 (35%) had undergone a hysterectomy because of insufficient improvement of complaints 5 patients underwent secondary hysterectomy (31% after successful UAE). HRQOL remained stable, without differences between groups. The urogenital distress inventory and the defecation distress inventory showed a decrease in both groups, probably related to increasing age, without significant differences between groups. Satisfaction in both groups remained comparable. The majority of patients declared being (very) satisfied about the received treatment: 78% of the UAE versus 87% in the hysterectomy group.

Goodwin et al. (2008) assessed the long-term clinical outcomes of uterine artery embolization across a wide variety of practice settings in 2112 patients with symptomatic leiomyomata. At 36 months after treatment, 1,916 patients remained in the study, and of these, 1,278 patients completed the survey. The primary measures of outcome were the symptom and health-related quality-of-life scores from the Uterine Fibroid Symptom and Quality of Life questionnaire. Mean symptom scores improved 41.41 points (P<.001), and the quality of life scores improved 41.47 points (P<.001), both moving into the normal range for this



questionnaire. The improvements were independent of practice setting. During the 3 years of the study, Kaplan-Meier estimates of hysterectomy, myomectomy, or repeat uterine artery embolization were 9.79%, 2.82%, and 1.83% of the patients, respectively. The investigators concluded that uterine artery embolization results in a durable improvement in quality of life.

## **Magnetic Resonance-Guided Focused Ultrasound Ablation (MRgFUS)**

A Hayes report concluded that, although evidence suggests that magnetic resonance-guided focused ultrasound (MRgFUS) reduces fibroid volume in women with symptomatic fibroids, the overall quality of the evidence is low due to the lack of well-designed controlled studies. Substantial uncertainty remains regarding the effect of magnetic resonance-guided focused ultrasound ablation of uterine fibroids on symptoms and the comparative effectiveness with other treatment alternatives. (Hayes, 2019)

In a clinical assessment, ECRI concluded the evidence for the ExAblate Body System was inconclusive. The evidence suggests that the ExAblate reduces symptoms and improves the quality of life (QOL) in women up to three years, however the studies have a high risk of bias and report on too few outcomes to be conclusive on how well it works. The evidence was limited by small sample size, retrospective design, high patient attrition, lack of control groups, randomization and blinding.

In a 2019 systematic review (included in Hayes report), Taheri et al. examined the change in uterine and fibroid volumes associated with uterine artery embolization (UAE), focused ultrasound (FUS), and radiofrequency ablation (RFA). Eighty-one relevant papers were identified: 52 related to UAE, 11 to RFA, 17 to FUS, 1 compared UAE and FUS. Uterine volume and fibroid volume changes seen in these studies were at 1 to 36 months. The pooled fibroid volume reductions at six months seen with RFA were 70%, UAE 54% and FUS 32%. All three types of nonresective treatment result in fibroid volume reduction. However, fibroid volume reduction is most marked with RFA, with UAE resulting in the next most volume reduction. Additional larger cohort studies, including those that are randomized and/or comparative, would enable definitive conclusions.

Verpalen et al. (2019, included in ECRI report) reassessed the effectiveness of Magnetic Resonance-High Intensity Focused Ultrasound (MRHIFU) on reducing fibroid related symptoms. Patients with fibroids containing a high T2 signal intensity or Funaki type 3 were excluded. Eighteen articles were included for review; sixteen of them were clinical trials and all were case series. The quality of evidence ranged from 9 to 16 using the 18-point criteria tool. The level of evidence for all included studies was IV according to Oxford Centre for Evidence-based Medicine (OCEBM) guidelines. Only 6 of the 18 studies were of acceptable quality. The author's concluded all studies displayed fibroid shrinkage and demonstrated that fibroids could continue shrink up to a years' time following the procedure. Adverse events were minimal and only two patients experience a serious adverse effect (DVT and third-degree skin burn). The studies suggested that MRHIFU may be a cost-effective strategy however the topic of cost was not analyzed. Limitations included weaknesses of a meta-analysis design, potential high-risk bias related to specific study designs, different sample sizes and loss of follow-up in some sub-studies. The authors expressed additional future studies are needed, but because randomized trials are difficult to conduct and pose methodological challenges along with difficulty recruiting patients, larger comparative controlled cohort studies with longer follow-up are warranted.

Ilerardi et al. (2018) performed a systematic review for percutaneous ablation on uterine fibroids. The primary endpoint was to investigate feasibility and safety of the technique. Six articles containing 541 patients was evaluated and no major complications of the procedure was found. After reviewing the data, the authors concluded microwave ablation of uterine fibroids to be safe and effective, however larger randomized prospective trials are needed to better demonstrate the benefits. The authors found a major limitation of MRgFUS is that many women are not eligible for the procedure due to potential challenges and risks associated with visceral injury.

Barnard et al. (2017, included in ECRI and Hayes reports) conducted a randomized controlled trial and comprehensive cohort analysis to compare the periprocedural outcomes of fibroid embolization and focused ultrasound. Premenopausal women with symptomatic uterine fibroids seen at 3 US academic medical centers were enrolled in the randomized controlled trial (n = 57). Women meeting identical criteria who declined randomization but agreed to study participation were enrolled in a nonrandomized parallel cohort (n = 34). The 2 treatment groups were analyzed by using a comprehensive cohort design. All women undergoing focused ultrasound and uterine artery embolization received the same post procedure prescriptions, instructions, and symptom diaries for comparison of recovery in the first 6 weeks. Return to work and normal activities, medication use, symptoms, and adverse events were captured with post procedure diaries. Data were analyzed using the Wilcoxon rank sum test or  $\chi^2$  test. Multivariable regression was used to adjust for baseline pain levels and fibroid load when comparing opioid medication, adverse events, and recovery time between treatment groups because these factors varied at

baseline between groups and could affect outcomes. Adverse events were also collected. The results showed focused ultrasound surgery was a longer procedure than embolization, with 23 (over half) women undergoing focused ultrasound 2 treatment days. Immediate self-rated post procedure pain was higher after uterine artery embolization than focused ultrasound. Compared with those having focused ultrasound (n = 39), women undergoing embolization (n = 36) were more likely to use outpatient opioid (75% vs 21%) and nonsteroidal anti-inflammatory medications (97% vs 67%) and to have a longer median recovery time (days off work, 8 vs 4; days until return to normal, 15 vs 10. There were no significant differences in the incidence or severity of adverse events between treatment arms; 86% of adverse events (42 of 49) required only observation or nominal treatment, and no events caused permanent sequelae or death. After adjustment for baseline pain and uterine fibroid load, uterine artery embolization was still significantly associated with higher opioid use and longer time to return to work and normal activities. Results were similar when restricted to the randomized controlled trial. The authors discussed the challenges that have inhibited mainstream adoption of MRgFUS and they include the prolonged duration of most procedures, patient eligibility with numerous exclusion criteria and restrictive selection criteria, and concluded that more comparative trials are needed to assess MRgFUS against other more established uterine-preserving treatments.

Havryliuk et al. (2017, included in Hayes report) conducted a systematic review and meta-analysis from clinical studies that described populations of pre-menopausal women seeking surgical management (both uterine-sparing and hysterectomy) for their symptomatic fibroids. Procedures included in the analysis were myomectomy, UAE, Lap-RFA, MRg-FUS, and hysterectomy. The complication rate for MRg-FUS was 6.0% (1.3% major; 5.1% minor) (N=298), and long-term follow-up averaged 12.6 months (N=209). The reintervention rate was highest of all the procedures at 30.5% (145 combined patients). Based on their analysis, the authors concluded that MRg-FUS carries low complication rates, no blood loss, and moderate improvement in HRQL scores. However, there is also a significant concern for injury of organs that may be in the way for focused ultrasound such as bowel, bladder, and sacral nerves. The authors state that limitations of this review include the inherent heterogeneity among studies; only a portion of the included studies were randomized controlled trials, most were not and were assigned an ACOG quality score of B; and lack of uniformity in reporting conventions. Further comprehensive prospective research, ideally in the form of well-powered randomized controlled trials, is needed to validate the specific treatment modality preferred for specific anatomical variances of fibroids.

In a pilot study (PROMISe), Jacoby et al. (2016, included in Hayes report) assessed the feasibility of a full-scale, randomized, placebo-controlled trial to evaluate the safety and efficacy of MRgFUS in premenopausal women with symptomatic uterine fibroids. Twenty women (mean 44 years of age) were enrolled. Thirteen were randomly assigned to MRgFUS and 7 to sham therapy. The primary outcome was a change in fibroid symptoms from baseline to 4 and 12 weeks after treatment assessed by the Uterine Fibroid Symptom Quality of Life Questionnaire (UFS-QOL). Secondary outcome was incidence of surgery or procedures for recurrent symptoms at 12 and 24 months. Four weeks after treatment, all participants reported improvement in the UFS-QOL: a mean of 10 points in the MRgFUS group and 9 points in the placebo group. By 12 weeks, the MRgFUS group had improved more than the placebo group (mean 31 points and 13 points, respectively). The mean fibroid volume decreased 18% in the MRgFUS group with no decrease in the placebo group at 12 weeks. After unblinding at 12 weeks, 5 patients in the sham group opted for treatment by MRgFUS and were followed for an additional 12 weeks. Two years after MRgFUS, 4 of 12 women who had a follow-up evaluation (30%) had undergone another fibroid surgery or procedure. The authors noted that a placebo effect may explain some of the improvement in fibroid-related symptoms observed in the first 12 weeks after MRgFUS. This study is limited by very small sample size and substantial loss to follow-up.

In a nonrandomized clinical trial, Froeling et al. (2013, included in Hayes report) compared the long-term outcome after uterine artery embolization (UAE) (n=41) versus magnetic resonance-guided high-intensity focused ultrasound (MR-g HIFU) (n=36) in women with symptomatic uterine fibroids. Symptom severity and total health-related quality of life scores were assessed by questionnaire before treatment and at long-term follow-up after UAE (median 61.9 months) and after MR-g HIFU (median: 60.7 months). Reintervention was significantly lower after UAE (12.2%) than after MR-g HIFU (66.7%) at long-term follow-up. The authors reported that improvement of symptom severity and health-related quality of life scores was significantly better after UAE resulting in a significant lower reintervention rate compared to MR-g HIFU.

In a prospective cohort study, Dobrotwir and Pun (2012) evaluated the efficacy and safety of MRgFUS in 100 patients (mean age 42 years) with symptomatic fibroids (n=104 treatments). Mean pretreatment fibroid volume was 185 cm<sup>3</sup> (range 2 to 1109). The authors reported that fibroid volume significantly decreased by the 12-month follow-up, and that the symptom severity score decreased by 55%. However, 14% of these patients required reintervention for persistent or recurrent fibroid disease. This study is limited by lack of randomization and control and short-term follow-up.

A retrospective study of 130 patients with symptomatic uterine leiomyomas treated with MRgFUS reported that the cumulative incidence of subsequent treatments for leiomyomas, such as hysterectomy or myomectomy, was 7.4% at 12-months. Patients were followed through retrospective review of medical records and phone interviews. At 3-, 6- and 12-month follow-up, 86% (90 of 105), 93% (92 of 99), and 88% (78 of 89) of patients reported relief of symptoms, respectively. Treatment-related complications were observed in 17 patients (13.1%): 16 patients had minor complications and one had a major complication (deep vein thrombosis). All complications were resolved within the 12-month follow-up period. This study is limited by its retrospective design (Gorny et al., 2011).

According to a systematic review prepared for the AHRQ, high intensity focused ultrasound 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 (Hartmann et al., 2017, included in Hayes report).

A National Institute for Health and Care Excellence (NICE) guidance document states that current evidence on the efficacy of MRgFUS for uterine fibroids in the short term is adequate, although further treatment may be required and the effect on subsequent pregnancy is uncertain. There are well-recognized complications, but the evidence on safety is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance and audit. NICE encourages further research into the efficacy of MRgFUS for uterine fibroids. Research studies should report long-term outcomes, including the need for further treatment (NICE, 2011).

## **Ultrasound-Guided Radiofrequency Ablation Procedures**

There is insufficient evidence to conclude laparoscopic or transcervical ultrasound-guided radiofrequency ablation procedures are effective for the treatment of fibroids. The body of evidence is low and additional research involving larger, randomized control trials is needed to establish their safety, efficacy and long-term outcomes.

Bradley et al. (2019) performed a systematic review and meta-analysis for treatment of fibroids with radiofrequency ablation (RFA). The authors identified 32 articles which included 1283 patients that were treated with either laparoscopic, transvaginal or transcervical RFA. It was hypothesized that RFA would significantly reduce fibroid volume and improve the patient's quality of life. The authors found that transcervical and transvaginal ablation were associated with a shorter length of stay on average and transcervical RFA had a faster return to normal activities when compared to laparoscopic RFA. Main strengths of the review included adherence to PRISMA guidelines, inclusion of almost 1300 patients and excellent generalization of results. The authors did conclude that RFA was effective for symptomatic uterine fibroids and improved the quality of life for patients. Limitations included lack of long-term data after 12 months, insufficient number of studies to perform statistical comparison among RFA delivery approaches and inability to determine if RFA efficacy was influenced by fibroid type or volume.

## ***Laparoscopic Ultrasound-Guided Radiofrequency Ablation***

A Hayes report evaluated the safety and efficacy of the Acessa System for treating uterine fibroids. Overall, a low-quality, limited body of evidence suggests that radiofrequency volumetric thermal ablation (RFVTA) consistently reduces the symptoms of uterine fibroids and improves health-related quality of life; however, substantial uncertainty exists regarding the comparative effectiveness and continued durability of this treatment. Limitations of the studies include small sample size, lack of a control group, limited follow-up and substantial attrition (Hayes, 2019).

An ECRI custom product brief regarding the Acessa™ system (Acessa Health, Inc.) concluded that limited evidence suggests that radiofrequency volumetric thermal ablation (RFVTA) improves symptoms and quality of life (QOL), and very limited evidence suggests that RFVTA offers minimally invasive, fertility-sparing uterine fibroid treatment. More randomized controlled trials (RCTs) are needed to elucidate RFVTA's best use (ECRI 2018).

Lin et al. (2019) conducted a meta-analysis assessing the short-term (3 and 6 months) and long-term (12, 24, and 36 months) symptom relief and quality of life improvement, procedure-related adverse event rate, reintervention rate, and days missed from work after laparoscopic radiofrequency ablation. Eight studies with a total of 581 patients were included in this review. Based on validated questionnaires, quality of life improved significantly until 36 months after laparoscopic radiofrequency ablation therapy, with a maximum improvement (Health-Related Quality of Life [HRQL] questionnaire score of +41.64 [95% confidence interval (CI), 38.94-44.34] and a transformed Symptom Severity Score [tSSS] of -39.37 [95% CI, 34.70-44.04]) at 12 months after laparoscopic radiofrequency ablation. All subscales of quality of life improved significantly, and most of the changes remained stable in long-term follow-up. The overall reintervention rate was 4.39% (95% CI, 1.60%-8.45%), and the median uterine volume

reduction was 69.17 cm<sup>3</sup> (95% CI, 35.87-102.46 cm<sup>3</sup>). The overall procedure-related adverse events rate was 1.78% (95% CI, 0.62%-3.53%), and patients missed an average of 4.35 days (95% CI, 2.55-6.15 days) of work. In conclusion, laparoscopic radiofrequency ablation therapy is an efficacious way to treat small-sized and nonpedunculated symptomatic uterine fibroids, providing stable long-term symptom relief and quality of life improvement with a low risk of adverse events and reintervention and just a few days of missed work. The authors identified several limitations. First, because most of the studies were non-comparative, differences in study types, inclusion and exclusion criteria, and study methodology were inevitable. Second, symptoms might be related to fibroid locations; however, not all studies classified patients by FIGO type, and so we could not analyze fibroids at different positions separately. In addition, the definition of procedure-related adverse events varied between studies, resulting in related data being based partially on the subjective judgment of the authors, not on objective definitions. Owing to the high loss to follow-up, the longest follow-up among the studies was 36 months. Therefore, long term follow-up data are still urgently needed.

In a systematic review and meta-analysis, Havryliuk et al. (2017) evaluated data from clinical studies that described populations of pre-menopausal women seeking surgical management (both uterine-sparing and hysterectomy) of their symptomatic fibroids. Procedures included in the analysis were myomectomy, UAE, Lap-RFA, MRg-FUS, and hysterectomy. Based on 209 patients (4 cohorts), the complication rate for Lap-RFA was overall 6.9% (1.7 major, 4.4% minor) with the reintervention rate 5.2%. Long-term follow-up averaged 27 months. The authors concluded that based on their analysis, Lap-RFA is associated with low complication rates, minimal EBL, and low reintervention rates. In addition, patients reported major improvement in their HRQL, and symptom severity scores compared to reports of more traditional interventions, such as hysterectomy, myomectomy, and UAE. Because of the precise placement of RF probe into a targeted myoma, which is confirmed by laparoscopic ultrasound before ablation, there is minimal disruption of normal myometrium and ovarian function. This is advantageous for patients who may desire future pregnancy. Pregnancy data are limited; however, normal full-term pregnancies resulting in vaginal deliveries have been reported after Lap-RFA. The authors state that limitations of this study include the inherent heterogeneity among studies; only a portion of the included studies were randomized controlled trials, most were not and were assigned an ACOG quality score of B; and lack of uniformity in reporting conventions. Further comprehensive prospective research, ideally in the form of well-powered randomized controlled trials, is needed to validate the specific treatment modality preferred for specific anatomical variances of fibroids.

Brucker et al. (2014, included in Hayes report and Bradley 2019 systematic review) conducted a randomized, single-center study comparing the perioperative outcomes of radiofrequency volumetric thermal ablation (RFVTA) and laparoscopic myomectomy (LM) in women who desired uterine conservation. Of 110 patients assessed for eligibility, 51 were randomized to the 2 interventions. The final analysis included 25 patients in the RFVTA group and 25 patients in the LM group. RFVTA resulted in the treatment of more fibroids, a significantly shorter hospital stay and less intraoperative blood loss than laparoscopic myomectomy. This study was sponsored by Halt Medical and is limited by small sample size and short-term follow-up.

At 12 months, Hahn et al. (2015, included in Hayes report and Bradley 2019 systematic review) reported similar clinical benefits in both groups. Mean symptom severity scores decreased (improved) by -7.8 for the ablation subjects and by -17.9 for the myomectomy subjects. Health-related quality of life improved (increased) by 7.5 and 13.1, respectively, for the two groups. Two myomectomy subjects had pregnancies that ended in a Cesarean delivery and a vaginal delivery of healthy infants. Two pregnancies in the RFVTA group ended in full-term vaginal deliveries of healthy infants.

At 24 months, Krämer et al. (2016, included in Hayes report and Bradley 2019 systematic review) reported improvements in the severity of symptoms from baseline by participants in both the RFVTA and LM groups. A significant improvement in health-related quality of life was observed in the LM group but not in the RFVTA group. A trocar-site hematoma occurred in one patient in the LM group. Further surgical interventions were recorded in three patients in the RFVTA group but these were unrelated to fibroid symptoms.

Galen et al. (2014, included in Bradley 2019 systematic review) performed a retrospective, multicenter clinical analysis of 206 consecutive cases of ultrasound-guided laparoscopic RFVTA of symptomatic uterine fibroids conducted under two phase II studies at 2 sites (n=69) and one phase III study at 11 sites (n=137). From baseline to 12 months in the phase II study, the mean transformed symptom severity scores improved from 53.9 to 8.8 (n=57), HRQOL scores improved from 48.5 to 92.0 (n=57) and mean uterine volume decreased from 204.4 cm<sup>3</sup> to 151.4 cm<sup>3</sup> (n=58). Patients missed a median of 4 days of work. The rate of possible device-related adverse events was 1.4%. In the phase III study, approximately 98% of patients were assessed at 12 months, and their transformed symptom severity scores, HRQOL scores, mean decrease in uterine volume and mean

menstrual bleeding reduction were also significant. Patients in phase III missed a median of 5 days of work. The rate of periprocedural device-related adverse events was 3.5%. This study is limited by retrospective design, lack of randomization and control and short-term follow-up.

Chudnoff et al. (2013, included in Hayes report and Bradley 2019 systematic review) reported preliminary results of a prospective clinical trial designed to evaluate laparoscopic ultrasound-guided radiofrequency volumetric thermal ablation for treating symptomatic uterine fibroids. The study clinically supported by Halt Medical, Inc. included a cohort of 135 premenopausal symptomatic women with uterine fibroids and objectively confirmed heavy menstrual bleeding. Primary outcome measures were menstrual bleeding at 12 months compared to baseline (pre-procedure), adverse events and surgical reintervention rates. At 3-, 6- and 12-month follow-ups, menstrual blood loss decreased from baseline levels by 31.8%, 40.7% and 38.3%, respectively. Symptom severity decreased from baseline and health-related quality of life improved. The authors reported one serious adverse event requiring readmission 5 weeks postprocedure and one surgical reintervention for persistent bleeding. Ninety-four percent of the women reported satisfaction with the treatment. This study is limited by lack of randomization and control and short-term follow-up.

Berman et al. (2014, included in Bradley 2019 systematic review) reported 3-year outcomes of 104 patients from the same trial. Questionnaire responses indicated sustained relief from symptoms and continued improvement in health-related quality of life through 36 months after ablation. The cumulative repeat intervention rate was 11% (14 of 135 participants) at 36 months. This study is supported by the study sponsor Halt Medical Inc., and limitations include lack of randomization and control.

In a systematic review prepared for AHRQ, Hartmann et al. (2017) found that the strength of evidence for radiofrequency ablation in the management of uterine fibroids is insufficient to inform care.

### ***Transcervical Ultrasound-Guided Radiofrequency Ablation***

In February 2019, Garza-Leal (included in Bradley 2019 systematic analysis) reported on the long-term (> 5 years) clinical outcomes of transcervical radiofrequency ablation of uterine fibroids. For this retrospective, single-arm, long-term data-collection study, 23 women with heavy menstrual bleeding secondary to fibroids were treated with transcervical radiofrequency ablation guided by integrated intrauterine sonography (using the Sonata<sup>®</sup> System, Gynesonics, Redwood City, CA). This study was within the 12-month Fibroid Ablation Study-EU clinical trial in Mexico. Symptoms were assessed using the Uterine Fibroid Symptom and Quality-of-Life's Symptom Severity Score (SSS) and Health-Related Quality of Life (HRQoL) subscales. Patients were queried regarding pregnancy and surgical reinterventions. The results showed seventeen women (73.9%) provided long-term follow-up information, with a mean of 64.4 months  $\pm$  4.5 months. From baseline, mean SSS decreased significantly from 64.9  $\pm$  16.9 to 27.6  $\pm$  36.1, and mean HRQoL improved significantly from 27.2  $\pm$  22.4 to 76.0  $\pm$  32.6 respectively. There were no surgical reinterventions through the first 3.5 years post-treatment. There was an 11.8% incidence of surgical reinterventions over 5.4 years of average follow-up, with 2 hysterectomies occurring after 3.5 and 4 years postablation, respectively (event rate: 2.2% per year; 95% confidence interval; 0.3%, 7.9%). Freedom from surgical reintervention at 1, 2, and 3 years was 100%, and, at 4 and 5 years, was 88.2%  $\pm$  7.8%. There was a single pregnancy occurring within the first year of treatment leading to a normal-term delivery by elective repeat cesarean section. The authors concluded that transcervical radiofrequency ablation with the Sonata System produced substantial durable clinical benefits beyond 5 years with a low reintervention rate. This study is limited by a lack of randomization and small number of participants and the results should be validated in larger patient populations.

Chudnoff et al. (2019, included in Bradley 2019 systematic review) conducted a prospective, multicenter, single-arm interventional trial of patients treated in the United States and Mexico, to evaluate the 12-month safety and effectiveness of transcervical ablation for the treatment of symptomatic uterine leiomyomas. Transcervical ablation using the Sonata System was performed on 1-10 leiomyomas in 147 patients with leiomyoma diameters ranging from 1 to 5 cm. Treated leiomyomas included all nonpedunculated types. Primary endpoints assessed at 12 months were reduction in menstrual blood loss and absence of surgical reintervention. Additional assessments included symptom severity, quality of life, patient satisfaction, reductions in uterine and leiomyoma volumes, and safety. The study met its primary endpoints at 12 months, because 64.8% of patients experienced 50% or greater reduction in menstrual bleeding and 99.3% of patients were free from surgical reintervention. The mean pictorial blood loss assessment chart score decreased by 38.9%, 48.4%, and 51.1% at 3, 6, and 12 months, respectively, and 95.1% of patients experienced a reduction in menstrual bleeding at 12 months. There were significant mean improvements in symptom severity and health-related quality of life of 32.1 points and 43.7 points, respectively, at 12 months. Mean maximal leiomyoma volume reduction per patient was 62.4%. More than half of patients returned to normal activity within 1 day, 96.3% of patients reported symptom improvement at 12 months, and 97% expressed

satisfaction with the treatment at 12 months. There were no device-related adverse events. The authors concluded that transcervical ablation was associated with a significant reduction in leiomyoma symptoms with no device-related adverse events and a low surgical reintervention rate through 12 months, demonstrating its potential to safely and effectively treat all nonpedunculated leiomyoma types through a uterus-conserving, incisionless approach.

Huirne and Brooks (2018) conducted a prospective, single-arm European trial in which 49 women with fibroids were treated with transcervical, intrauterine ultrasound-guided radiofrequency ablation with the Sonata System. The EQ-5D-3L system was utilized to collect patient health status at baseline, 3, 6, and, 12 months post-procedure. Patient-reported health states at each time point were converted into a health utility value using time-trade off methodology. Patient health utility increased from a mean of 0.745 at baseline, to means of 0.838, 0.852, and 0.914 at 3 months, 6 months, and 12 months, respectively. The change from baseline at 12 months was significant. Randomized controlled trials with larger patient populations and longer follow-up periods are needed to further evaluate the Sonata system.

Bongers et al. (2015, included in Bradley 2019 systematic review) conducted a prospective, longitudinal, multicenter, single-arm controlled trial to establish the effectiveness and confirm the safety of transcervical, intrauterine, ultrasound-guided radiofrequency ablation in the treatment of uterine fibroids. Fifty consecutive women with symptomatic uterine fibroids (n=92 fibroids) received treatment with the VizAblate System. The primary study endpoint was the percentage change in perfused fibroid volume at 3 months. Secondary endpoints, reached at 6 months, included safety, symptom reduction, rate of surgical reintervention and number of days to return to normal activity. Perfused fibroid volumes were reduced at 3 months by an average of  $68.8 \pm 27.8\%$ . Six-month results suggest that the VizAblate System is safe and effective in providing relief of abnormal uterine bleeding associated with fibroids, with appropriate safety and a low reintervention rate. Similar results were reported at 12 months (Brölmann et al., 2016).

Garza-Leal et al. (2011) conducted a single center cohort study to evaluate the safety of the VizAblate transcervical device for the treatment of uterine fibroids. Nineteen women with uterine fibroids received treatment with the VizAblate System in a closed abdomen setting prior to hysterectomy. Twelve women underwent an immediate abdominal hysterectomy after radiofrequency ablation (acute group), while the remaining seven underwent hysterectomy on post-ablation days 16 and 17 (subacute group). Uteri were analyzed to quantify fibroid ablation dimensions and assess the serosa for thermal injury. Subjects in the subacute group were treated under conscious sedation and indicated overall procedural satisfaction. There were no complications or thermal serosal injury. For women in the subacute group receiving one ablation, the mean total procedure time was  $25.8 \pm 6.0$  minutes (range 18–32 minutes). All subjects in the subacute group were discharged within 2 hours of the procedure. For fibroids  $\leq 5$  cm,  $67.2\% \pm 27.0\%$  of the fibroid volume was ablated (range 15–100%; median 75%). The authors concluded that transcervical radiofrequency ablation of fibroids under intrauterine sonographic guidance with the VizAblate system can be accomplished with a high degree of reliability and without adverse events.

Toub (2017) evaluated the clinical evidence for the Sonata System, the results of which showed significant median reductions in total (73.3%) and perfused (73.3%) uterine fibroid volume, menstrual bleeding (72.3%), symptom severity (62.5%), and improvements in health-related quality of life (127%) at 12 months post-ablation. In the author's opinion, the Sonata System is a promising treatment modality for uterine fibroids that does not require general anesthesia or hospitalization, and has the potential for redefining the current paradigm for management of symptomatic fibroids. Randomized controlled trials with longer follow-up periods are needed to evaluate the safety and reliability of this procedure.

## Clinical Practice Guidelines

### *American College of Obstetricians and Gynecologists (ACOG)*

An ACOG committee opinion on acute abnormal uterine bleeding concludes that surgical management should be considered for patients who are not clinically stable, are not suitable for medical management or have failed to respond appropriately to medical management. The choice of surgical management should be based on the patient's underlying medical conditions, underlying pathology and desire for future fertility. The report also mentions the use of levonorgestrel-releasing IUDs as an option for the long-term treatment of chronic AUB (ACOG, 2013; reaffirmed 2017).

### Levonorgestrel-Releasing Intrauterine Device

An ACOG practice bulletin on the use of noncontraceptive uses of hormonal contraceptives states the following:

- Combined oral contraceptives (OC) have been shown to regulate and reduce menstrual bleeding, treat dysmenorrhea, reduce premenstrual dysphoric disorder symptoms and ameliorate acne. (Evidence Level A – Based on good and consistent scientific evidence.)
- Hormonal contraception should be considered for the treatment of menorrhagia in women who may desire further pregnancies (ACOG, 2010; reaffirmed 2016). (Evidence Level B – Based on limited or inconsistent scientific evidence.)

In a practice bulletin on alternatives to hysterectomy in managing uterine fibroids, ACOG states that the levonorgestrel intrauterine system leads to minimal systemic effects, and the localized endometrial effect is beneficial for treatment of menorrhagia. Small studies suggest that the levonorgestrel intrauterine system may be effective for treatment of heavy uterine bleeding in women with leiomyomas. However, these women may have a higher rate of expulsion and vaginal spotting (ACOG, 2008; reaffirmed 2016).

### **Uterine Artery Embolization**

In a practice bulletin on alternatives to hysterectomy in managing uterine fibroids, ACOG states that based on long- and short-term outcomes, uterine artery embolization is a safe and effective option for appropriately selected women who wish to retain their uteri (ACOG, 2008; reaffirmed 2016).

In a practice bulletin for abnormal uterine bleeding (AUB), ACOG states an office endometrial biopsy is the first-line procedure for tissue sampling in the evaluation of patients with AUB. Endometrial sampling should be performed on patients younger than 45 years of age for persistent AUB and failed medical management. (ACOG 2012, reaffirmed 2016).

### **Magnetic Resonance Imaging-Guided Focused Ultrasound Ablation**

In a practice bulletin on alternatives to hysterectomy in managing uterine fibroids, ACOG states that while short-term studies show safety and efficacy, long-term studies are needed to discern whether the minimally invasive advantage of MRgFUS will lead to durable results beyond 24 months (ACOG, 2008; reaffirmed 2016).

### ***American Association of Gynecologic Laparoscopists (AAGL)***

In a position statement on the treatment of submucous leiomyomas, the AAGL (2012) states that with currently available evidence, embolic and ablative therapies are not appropriate for women with submucous myomas who have current infertility or who wish to conceive in the future. These techniques include UAE and occlusion, as well as leiomyoma ablation with radiofrequency electricity, cryotherapy, and MRg-FUS (based primarily on consensus and expert opinion [Level C]). The AAGL recommends long-term studies on the impact of various ablation techniques on the symptom of HMB in women with submucous leiomyomas.

### ***American College of Radiology (ACR)***

ACR appropriateness criteria conclude the following:

- Uterine artery embolization (UAE) is effective in managing symptomatic uterine fibroids.
- UAE and myomectomy have similar clinical success and complication rates.
- There is little long-term information on the efficacy of MRgFUS.
- A full gynecologic workup, including a Pap smear every 3 years and/or an endometrial biopsy if a patient has menometrorrhagia before UAE is performed (ACR, 2018).

### ***American Academy of Family Physicians***

An endometrial biopsy is an office procedure that serves as a helpful tool in diagnosing various uterine abnormalities. Endometrial biopsy is a safe and accepted method for the evaluation of abnormal or postmenopausal bleeding. The procedure is often performed to exclude the presence of endometrial cancer or its precursors such as abnormal uterine bleeding (Zuber 2001).

### ***Society of Interventional Radiology (SIR)***

SIR quality improvement guidelines (Dariushnia et al., 2014) state that uterine artery embolization is indicated for the treatment of uterine leiomyomata that are causing significant symptoms, occasionally a single symptom, but more commonly a combination of symptoms. The most common of these are:

- Heavy or prolonged menstrual bleeding

- Severe menstrual cramping
- Pelvic pressure, discomfort, excessive bloating or fullness, particularly perimenstrual, or bothersome abdominal wall distortion caused by the enlarged uterus
- Pelvic pain related to identified leiomyomas, including dyspareunia
- Urinary urgency, frequency, nocturia or retention related to the enlarged leiomyomatous uterus
- Hydronephrosis caused by the enlarged uterus

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

### Levonorgestrel-Releasing Intrauterine Device

Mirena® received FDA approval on December 8, 2000 for use as an intrauterine contraceptive. Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception was approved as an additional indication on October 1, 2009. Search the following website for more information:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. (Accessed July 2, 2020)

Skyla® received FDA approval on January 9, 2013 for use as an intrauterine contraceptive. Search the following website for more information: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. (Accessed July 2, 2020)

Liletta™ received FDA approval on February 26, 2015 for use as an intrauterine contraceptive. Search the following website for more information: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. (Accessed July 2, 2020)

Kyleena™ received FDA approval on September 16, 2016 for use as an intrauterine contraceptive. Search the following website for more information: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. (Accessed July 2, 2020)

### Uterine Artery Embolization

Uterine artery embolization (UAE) is a procedure and, therefore, not subject to FDA regulation. However, the embolic agents used are subject to FDA oversight. A number of agents are approved by the FDA for embolization procedures of the neurological system, but several have been specifically approved for UAE. Search the following website for additional information: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. (Accessed July 2, 2020)

### Magnetic Resonance-Guided Focused Ultrasound (MRgFUS)

The ExAblate 2000/2100 System (Insightec) received premarket approval (PMA) on October 22, 2004 (P040003); approval for updated labeling was given on August 9, 2011. The device is indicated for ablation of uterine fibroid tissue in pre- or perimenopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure and whose uterine size is less than 24 weeks. On August 31, 2015, the indications were modified to remove the restriction of treatment to women who had completed childbearing. See the following website for more information:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P040003S009> (Accessed July 2, 2020)

### Laparoscopic Ultrasound-Guided Radiofrequency Ablation

The Acessa System received FDA clearance for marketing on November 5, 2012 (K121858). The device is indicated for use in percutaneous, laparoscopic coagulation and ablation of soft tissue, including treatment of symptomatic uterine fibroids under laparoscopic ultrasound guidance. See the following website for additional information:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K132744>. (Accessed July 2, 2020)

The Acessa ProVu System, the next generation of the Acessa System, received FDA clearance on September 28, 2018. It is indicated for use in percutaneous, laparoscopic coagulation and ablation of soft tissue, including treatment of symptomatic uterine fibroids under laparoscopic ultrasound guidance. See the following website for additional information:

[https://www.accessdata.fda.gov/cdrh\\_docs/pdf18/K181124.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf18/K181124.pdf). (Accessed July 2, 2020)

The Sonata® Sonography-Guided Transcervical Fibroid Ablation System received FDA clearance for marketing on August 15, 2018. This device is intended for diagnostic intrauterine imaging and transcervical treatment of symptomatic uterine fibroids,



including those associated with heavy menstrual bleeding. See the following website for additional information:  
[https://www.accessdata.fda.gov/cdrh\\_docs/pdf17/K173703.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf17/K173703.pdf). (Accessed July 2, 2020)

## Laparoscopic Power Morcellation Warning

A February 25, 2020 FDA Safety Communication recommends performing laparoscopic power morcellation for myomectomy or hysterectomy only with a tissue containment system (legally marketed in the U.S.) for use during laparoscopic power morcellation and performing only in appropriately selected patients.

See the following website for additional information:

<https://www.fda.gov/medical-devices/safety-communications/update-fda-recommends-performing-contained-morcellation-women-when-laparoscopic-power-morcellation>. (Accessed July 16, 2020)

A November 24, 2014 FDA Safety Communication recommends that manufacturers of laparoscopic power morcellators with a general indication or a specific gynecologic indication prominently include the following black box warning and contraindications in their product labeling:

### *Warning*

Uterine tissue may contain unsuspected cancer. The use of laparoscopic power morcellators during fibroid surgery may spread cancer, and decrease the long-term survival of patients. This information should be shared with patients when considering surgery with the use of these devices.

### *Contraindications*

- Laparoscopic power morcellators are contraindicated in gynecologic surgery in which the tissue to be morcellated is known or suspected to contain malignancy.
- Laparoscopic power morcellators are contraindicated for removal of uterine tissue containing suspected fibroids in patients who are peri- or post-menopausal, or are candidates for en bloc tissue removal, for example through the vagina or via a mini-laparotomy incision.

See the following website for additional information:

<http://www.fda.gov/downloads/MedicalDevices/Safety/AlertsandNotices/UCM424444.pdf>. (Accessed July 16, 2020)

In December 2017, the FDA released new findings on the risks of spreading hidden uterine cancer through the use of laparoscopic power morcellators which suggests that approximately 1 in 225 to 1 in 580 women who undergo surgery (hysterectomy or myomectomy) for presumed benign uterine growths may have occult or hidden uterine cancers known as sarcomas. This is generally consistent with the 1 in 350 incidence estimated by the FDA in a 2014 review. The FDA also estimates the rate of occult leiomyosarcoma, a particularly aggressive type of sarcoma, to be approximately 1 in 495 to 1 in 1100, again in general agreement with our previous assessment of 1 in 498. Ranges in incidence represent estimates based on differing statistical analyses of available study data.

A white paper published in December 2017 provides an update on medical device reports the FDA received through April 2017 related to the use of laparoscopic power morcellators and how hysterectomy and myomectomy procedure selection has changed since the FDA's 2014 warning against the routine use of morcellators to treat suspected uterine fibroids. This data demonstrates that overall, use of laparoscopic power morcellators has decreased since the FDA warned about it in 2014.

See the following website for additional information:

<https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/UCM584539.pdf>. (Accessed July 16, 2020)

## Transcervical Ultrasound-Guided Radiofrequency Ablation

The Sonata® Sonography-Guided Transcervical Fibroid Ablation System received FDA 510(k) marketing clearance on August 15, 2018. It is intended for diagnostic intrauterine imaging and transcervical treatment of symptomatic uterine fibroids, including those associated with heavy menstrual bleeding. See the following website for additional information:  
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K173703>. (Accessed July 16, 2020)

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## Policy History/Revision Information

Date	Summary of Changes
07/01/2021	<b>Coverage Rationale</b> <ul style="list-style-type: none"><li>Replaced reference to “InterQual® 2020” with “InterQual® 2021”</li></ul> <b>Supporting Information</b> <ul style="list-style-type: none"><li>Archived previous policy version CS002KY.01</li></ul>

## Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state, or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare uses InterQual® for the primary medical/surgical criteria, and the American Society of Addiction Medicine (ASAM) for substance use, in administering health benefits. If InterQual® does not have applicable criteria, UnitedHealthcare may also use UnitedHealthcare Medical Policies, Coverage Determination Guidelines, and/or Utilization Review Guidelines that have been approved by the Kentucky Department for Medicaid Services. The UnitedHealthcare Medical Policies, Coverage Determination Guidelines, and Utilization Review Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.