

# ABNORMAL UTERINE BLEEDING AND UTERINE FIBROIDS

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## INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care 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.

## CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General benefits package
Referral Required (Does not apply to non-gatekeeper products)	Yes - Office <sup>2</sup> No - Inpatient <sup>1</sup> , Outpatient <sup>1</sup>
Authorization Required (Precertification always required for inpatient admission)	Yes - Inpatient, Outpatient No - Office <sup>1,2</sup>
Precertification with Medical Director Review Required	No <sup>1,2</sup>
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Inpatient, Outpatient, Office <sup>2</sup>
Special Considerations	<sup>1</sup> Review by a Medical Director or their designee is required <b>only</b> for CPT codes 0071T, 0072T, 0404T, 37243, 58578, 58674, and 58999 in all sites of service. <sup>2</sup> <b>Participating Providers in the Office Setting:</b> Precertification is required for CPT codes 0071T, 0072T, 0404T, 37243, 58578, 58674 and 58999 when

Special Considerations  
(continued)

performed in the office of a participating provider.  
**Non-Participating/Out-of-Network Providers in the Office Setting:** Precertification is not required, but is encouraged for CPT codes 0071T, 0072T, 0404T, 37243, 58578, 58674, and 58999 for out-of-network services performed in the office. If precertification is not obtained, Oxford will review for out of network benefits and medical necessity after the service is rendered.

## BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some plan documents exclude benefit coverage for contraception. In those plan documents, coverage for intrauterine devices (IUD), including the levonorgestrel-releasing intrauterine device (LNG-IUD), is excluded when used for contraceptive purposes. However, in those plan documents, coverage exists for the levonorgestrel-releasing intrauterine device (LNG-IUD) when used for a non-contraceptive purpose, including treatment of abnormal uterine bleeding, when supported by clinical evidence.

Most plan documents provide coverage for unproven and not medically necessary services for a life-threatening sickness or condition, at our discretion. Additionally, some plan documents may provide coverage for unproven and not medically necessary services under certain non-life-threatening conditions at our discretion. Magnetic resonance-guided focused ultrasound (MRgFUS) is a covered service for certain benefit plans. Other terms and conditions to claims payment may apply, depending on the terms of the member specific benefit plan document, a provider's participation agreement and the *Oxford Supplement* to the UnitedHealthcare *Administrative Guide*. Providers should refer to the current *Oxford Commercial Supplement* to the UnitedHealthcare *Administrative Guide* for additional details, available at [uhcprovider.com](http://uhcprovider.com) > Menu > [Administrative Guides and Manuals](#).

### **Essential Health Benefits for Individual and Small Group**

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

## COVERAGE RATIONALE

### **Levonorgestrel-Releasing Intrauterine Device**

**Levonorgestrel-releasing intrauterine devices (LNG-IUD) (e.g., Mirena<sup>®</sup>, Skyla<sup>®</sup>, Liletta<sup>®</sup> or Kyleena<sup>™</sup>) are proven and/or medically necessary for treating menorrhagia.**

See the [U.S. Food and Drug Administration \(FDA\)](#) section below for additional information.

### **Uterine Fibroids**

**Uterine artery embolization (UAE) is proven and/or medically necessary for treating symptomatic uterine fibroids for women who do NOT wish to preserve their childbearing potential which has been documented and confirmed in the medical record.**

For information regarding medical necessity review, when applicable, see MCG<sup>™</sup> Care Guidelines, 22<sup>nd</sup> edition, 2018, Uterine Artery Embolization, ACG: A-0287 (AC).

**Uterine artery embolization (UAE) is unproven and/or not medically necessary for treating symptomatic uterine fibroids for women who wish to preserve their childbearing potential.**

The effects of UAE on ovarian and uterine function and on fertility require further studies of safety and/or efficacy in published, peer-reviewed medical literature.

**Magnetic resonance guided focused ultrasound ablation (MRgFUS) is unproven and/or not medically necessary for treating uterine fibroids.**

Further studies are needed to determine the long-term efficacy of this procedure and to evaluate the efficacy and safety of this procedure relative to other treatment options for uterine fibroids. See the [Benefit Considerations](#) section for potential coverage of unproven services.

**Laparoscopic ultrasound-guided radiofrequency ablation (e.g., Acessa™) is unproven and/or not medically necessary for treating uterine fibroids.**

Further well-designed randomized controlled trials are needed to determine the long-term efficacy of this procedure and to evaluate the efficacy and safety of this procedure relative to other treatment options for uterine fibroids.

**Transcervical ultrasound-guided radiofrequency ablation is investigational, unproven and/or not medically necessary for treating uterine fibroids due to lack of FDA approval.**

Further studies are needed to determine the long-term efficacy of this procedure and to evaluate the efficacy and safety of this procedure relative to other treatment options for uterine fibroids.

**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 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)

*CPT® is a registered trademark of the American Medical Association*

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

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.

Conservative management of symptomatic fibroids includes watchful waiting and hormonal therapy. Hormone therapy may cause the fibroids to shrink; however they will quickly return to their original mass once therapy has been discontinued. Hysterectomy has been the primary treatment for symptomatic or rapidly enlarging fibroids.

Hysteroscopic removal of fibroids has been the procedure of choice for those women who want to maintain their fertility, but this is a demanding and lengthy procedure and sometimes more difficult to perform than a hysterectomy and does not prevent the recurrence of fibroids. The resulting endometrial cavity may be problematic for fertility.

Alternate minimally invasive techniques have emerged. An advantage of these procedures over hysterectomy is that they do not involve surgical removal of the uterus; therefore, the operative and recovery times are shorter and the complication rates seem to be lower. Some may be performed as outpatient procedures, avoiding the hospital stay required after hysterectomy.

#### **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 MRI-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.

#### **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.

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%).

There is evidence from several randomized controlled trials and a few nonrandomized controlled trials and prospective case series that the LNG-IUD is a relatively safe and efficacious minimally invasive therapy for AUB in premenopausal women with confirmed menorrhagia that is refractory to oral medications or for whom surgery has been recommended, who have no benign or malignant pelvic pathology that requires another type of therapy, who do not want or are ineligible for surgery, who cannot tolerate the drug side effects and/or who wish to retain their childbearing capacity. Overall, treatment with the LNG-IUD for 3 to 12 months resulted in significant reductions in menstrual blood loss (MBL) (ranging from 67% to 96%), improvement in menstrual bleeding patterns in the majority of patients, increases in blood hemoglobin and iron levels, high levels of satisfaction and improved quality of life (QOL). Surgery was cancelled or postponed in approximately 70% of patients on surgical waiting lists whose menstrual bleeding improved during LNG-IUD therapy. The rates of treatment discontinuation or failure varied from 3% to 52%. (Hurskainen, 2001; Lahtenmaki, 1998; Istre, 2001; Crosignani, 1997; Barrington, 1997; Fedele, 1997; and Romer, 2000)

The evidence from the randomized controlled trials comparing the LNG-IUD with drug therapy (the progestin norethisterone, an NSAID and an antifibrinolytic) showed that the IUD reduced MBL by over 90% and induced amenorrhea in 32% to 44% of patients. While patients were more satisfied with the LNG-IUD than with oral norethisterone, and no serious side effects were reported, IUD use was associated with a higher incidence of spotting and intermenstrual bleeding at 3 months. While spotting and intermenstrual bleeding are initially common following



insertion of the LNG-IUD, these symptoms tend to lessen or disappear. LNG-IUD was significantly more efficacious than the NSAID flurbiprofen and the antifibrinolytic tranexamic acid for reducing MBL and improving blood Hb and ferritin levels; however, the IUD was removed in 15% of patients due to side effects or persistent menorrhagia, and 5% of patients had a hysterectomy after device expulsion. No major side effects were associated with the LNG-IUD. (Hurskainen, 2001; Lahteenmaki, 1998; Istre, 2001; Crosignani, 1997; Barrington, 1997; Fedele, 1997; and Romer, 2000)

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 was 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.

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. The LNG-IUD was less effective than hysterectomy in reducing HMB.

Busfield et al. (2006) compared LNG-IUD (n=40) to thermal balloon ablation (n=39) in a prospective, randomized trial. Both treatments resulted in significant reductions in pictorial bleeding assessment chart (PBAC) scores. However at 12 and 24 months, median PBAC scores in women treated by LNG-IUD were significantly lower than those of women treated by thermal balloon (11.5 versus 60.0 and 12.0 versus 56.5, respectively) supporting LNG-IUD as more efficacious. Treatment failed in 11 (28%) women using the LNG-IUD and in 10 (26%) women treated with thermal balloon ablation.

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, 2018)

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

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 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. 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.

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.

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.

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.

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 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 (2018) 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. Most studies involve the same patient population studied in the pivotal trial sponsored by the manufacturer. In addition, there is no published data comparing this procedure to other uterus-sparing treatments such as myomectomy or uterine artery embolization. Additional long-term studies, particularly randomized controlled trials that compare outcomes following MRgFUS with other therapies, are needed before definitive conclusions can be drawn regarding effectiveness of this technology. (Hayes, 2017)

In a pilot study (PROMISE), Jacoby et al. (2016) 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.

A manufacturer-sponsored, multicenter, prospective uncontrolled clinical trial evaluated the efficacy and safety of MRgFUS including symptom relief and quality of life (QOL) in 109 patients who were otherwise candidates for hysterectomy due to the severity of their symptoms. The results were published in several studies. At 6 months, Hindley et al. (2004) reported that 79.3% of women who had been treated reported a significant improvement in their uterine fibroid symptoms on follow-up health-related quality-of-life questionnaires. The mean reduction in fibroid volume was 13.5%, but nonenhancing volume remained within the treated fibroid. The authors concluded that despite the small change in the volume of treated tumors, the improvement in symptoms was meaningful.

Stewart et al. (2006) reported outcomes in 82 of the original patient population. Fifty-one percent of women who had been treated reached the targeted symptom reduction. The magnitude of improvement was greater than predicted, with subjects having a mean volume decrease of 36%. A modest volume reduction similar in magnitude to the treated volume was seen. The authors concluded that the rate of symptom relief was fairly high considering that only 10% of the fibroid volume was treated on average due to the strict treatment guidelines. They added that this undertreatment may have accounted for the need for alternative therapy in 28% of patients. At 3 years, Kim et al. (2011) evaluated outcomes in 29 of the original patient population. The results showed sustained symptomatic relief among enrolled patients. The mean volume decrease was 32.0%. Thirty-one percent sought alternative treatments due to inadequate control of symptoms. There were no long-term complications. The authors concluded that, although the results are preliminary, MRgFUS for the treatment of uterine fibroids may result in acceptable long-term outcomes at 3 years. Limitations of these studies include lack of randomization and control, no comparison of MRgFUS to other minimally invasive technologies intended to treat uterine fibroids and small sample size.

In a nonrandomized clinical trial, Froeling et al. (2013) 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)

Taran et al. (2009) compared women undergoing MRgFUS to a group of contemporaneously recruited women undergoing total abdominal hysterectomy. Patient demographics, safety parameters, quality of life outcomes and disability measures are reported. One hundred and nine women were recruited in seven centers for MRgFUS treatment and 83 women who underwent abdominal hysterectomy were recruited in seven separate centers to provide contemporaneous assessment of safety. Overall, the number of significant clinical complications and adverse events was lower in women in the MRgFUS group compared to women undergoing hysterectomy. MRgFUS was associated with significantly faster recovery, including resumption of usual activities. At 6 months of follow-up, there were four (4%) treatment failures in the MRgFUS arm. There was improvement in all quality of life scales for both treatment groups at 6 months. However, scores were significantly better in the hysterectomy group than in the MRgFUS group. Women undergoing MRgFUS had steady improvement in all parameters throughout the 6-month follow-up period, despite the fact that they continued to have symptomatic myomatous uteri and menstruation. The authors concluded that MRgFUS treatment of uterine leiomyomas leads to clinical improvement with fewer significant clinical complications and adverse events compared to hysterectomy at 6 months' follow-up. Longer follow-up from randomized trials is needed to confirm these results.

In a prospective cohort study, Funaki et al. (2009) assessed the efficacy of MRgFUS in women with symptomatic myomas who otherwise would have been treated with conventional surgery. The study included 91 premenopausal Japanese patients (mean age 40.4 years) with 141 fibroids measuring 4 to 10 cm in diameter. Fibroids were characterized by their appearance on MR images as type 1 (low intensity similar to that of skeletal muscle) (n=25 patients; mean fibroid volume 129.0 cm<sup>3</sup>, range 14.4 to 724.1), type 2 (intermediate intensity between that of myometrium and skeletal muscle) (n=55 patients; mean fibroid volume 211.7 cm<sup>3</sup>, range 14.9 to 757.7) and type 3 (high intensity, ≥ that of myometrium) (n=11 patients; mean fibroid volume 180.8 cm<sup>3</sup>; range 34.6 to 501.9). The follow-up time was 24 months. The authors found that patients with type 1 or 2 fibroids had a significant reduction in the symptom severity score at 3 months, which was sustained at 2 years. However, nearly 16% of the 80 patients with type 1 or 2 fibroids required reintervention. MRgFUS was ineffective in 11 patients with type 3 fibroids. This study is limited by lack of randomization and control.

Havryliuk et al. (2017) 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.

Additional systematic reviews for the treatment of uterine fibroids with MRg-FUS (Ierardi et al., 2018; ), list potential challenges and risks with this procedure including adjacent visceral injury (e.g., bowel, bladder), nerve damage, procedure length, and high failure rate potentially due to incomplete treatment, resulting in re-intervention (Gingold et al., 2018). Laughlin-Tommaso (2017) estimates that symptom improvement occurs in approximately 80% of women undergoing MRg-FUS, with a reintervention rate of 23% at 4 years post-procedure. Age less than 45 years, low NPV ratio, and myomas that have signs of increased vascularity (such as bright myomas on T2-weighted images)

have less improvement. Although early case series show encouraging pregnancy outcomes, clinical experience in achieving and managing pregnancy after MRg-FUS is limited. (Gingold et al., 2018; Harvyliuk et al., 2017)

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)

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 MRgFUS for uterine fibroids. Research studies should report long-term outcomes, including the need for further treatment. (NICE, 2011)

### **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, 2017)

Brucker et al. (2014) 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) 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) 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) 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) 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 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.

At 24 months, Guido et al. (2013) reported significant improvements in symptom severity scores and health-related quality of life in 112 premenopausal women with symptomatic uterine fibroids and confirmed heavy menstrual

bleeding. Improvements occurred more readily between baseline and 3 months compared with any other follow-up period (e.g., 6, 12, and 24 months). A reintervention rate of 4.8% was reported due to fibroid-related bleeding between 12 and 24 months. This study is also limited by lack of randomization and control.

Berman et al. (2013) 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 also limited by lack of randomization and control.

Gingold et al. (2018) conducted a review of minimally invasive approaches to myoma management, and concluded that UAE, MRg-FUS, and RFA remain promising alternatives to hysterectomy and laparoscopic myomectomy. In their opinion, RFA in particular has the opportunity to become more widely used as it avoids the need for myoma enucleation and laparoscopic suturing. The authors recommend future studies in evaluating effects of alternative surgical approaches to pregnancy outcomes.

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.

In a systematic review of nonsurgical management of myomas, Laughlin-Tommaso (2017) summarized that for radiofrequency volumetric thermal ablation, symptom relief as demonstrated by a high decrease in symptom severity, and increase in quality of life scores is maintained out to 3 years post-procedure. Overall reintervention rate at 3 years has been estimated at 11% in the initial trials.

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.

In a small case series, Robles et al. (2013) assessed the safety and efficacy of laparoscopic radiofrequency volumetric thermal ablation (RFVTA) in women with symptomatic uterine fibroids. Thirty-five premenopausal women (ages 33-51 years) with symptomatic fibroids were enrolled and followed for 12 months. Uterine fibroid symptom and health-related quality-of-life (UFS-QOL) questionnaires were completed at 0, 3, 6 and 12 months. Symptom severity scores reduced significantly: baseline (63.3), 3 months (23.1), 6 months (15.4), 12 months (9.6). Health-related quality-of-life scores significantly: baseline (37.3), 3 months (79.9), 6 months (85.1), 12 months (87.7). Nine adverse events among 8 individuals were minor and unrelated to the procedure. This study is limited by lack of randomization and control, short-term follow-up and small sample size.

In another small case series, 31 women (ages 28 to 51 years) with symptomatic uterine fibroids who desired uterine preservation underwent outpatient laparoscopic, ultrasound-guided, radiofrequency volumetric thermal ablation using the Halt 2000 System. Postoperative follow-up occurred at 3, 6 and 12 months. The primary outcome measures were patient safety, frequency of adverse events, repeat intervention rate, symptom severity and health-related quality-of-life scores from the validated Uterine Fibroid Symptom and Quality-of-Life Questionnaire. Secondary outcome measures were uterine volume changes over time. At 3, 6 and 12 months, respectively, mean symptom severity scores improved significantly compared with baseline, by 59.7%, 71.7% and 82.0%. The increase in mean health-related quality-of-life scores over time reached statistical significance: 60.15 at baseline, 87.9 at 3 months, 90.8 at 6 months and 97.8 at 12 months. Mean (SD) uterine volume decreased from 194.4 at baseline to 159.5 at 3 months, 147.2 at 6 months and 113.2 at 12 months. There were no procedure-related repeat hospitalizations, repeat treatments or any procedures related to fibroid symptoms following treatment. This study is limited by lack of randomization and control, short-term follow-up and small sample size. The authors concluded that additional larger multicenter studies are needed to confirm these results. (Garza et al., 2011)



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

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) 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.

The Sonography Guided Transcervical Ablation of Uterine Fibroids (SONATA) phase III clinical trial is ongoing and designed to evaluate the safety and efficacy of this device system in the treatment of symptomatic uterine fibroids. ClinicalTrials.gov Identifier: NCT02228174.

## **Professional Societies**

### ***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)

### **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 submucosal uterine fibroids, 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. (ACR, 2009; last review date 2017)

### **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)**

### **Levonorgestrel-Releasing Intrauterine Device**

Mirena<sup>®</sup> 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 May 11, 2018)

Skylla<sup>™</sup> received FDA approval on January 9, 2013 for use as an intrauterine contraceptive only. Search the following website for more information: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. (Accessed May 11, 2018)

Liletta<sup>™</sup> received FDA approval on February 26, 2015 for use as an intrauterine contraceptive only. Search the following website for more information: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. (Accessed May 11, 2018)

Kyleena<sup>™</sup> 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 May 11, 2018)

### **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 May 11, 2018)

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

The ExAblate 2000 System (Insightec) received premarket approval (PMA) on October 22, 2004 (P040003). 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=P040003>. (Accessed May 11, 2018)

### **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:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K121858>. (Accessed May 11, 2018)

### **Laparoscopic Power Morcellation Warning**

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 May 11, 2018)

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

The Sonata™ System, with VizAblate® technology, has not yet received FDA approval and is limited to investigational use in the United States.

## **REFERENCES**

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by the UnitedHealthcare Medical Technology Assessment Committee. [2018T0442AA]

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**POLICY HISTORY/REVISION INFORMATION**

Date	Action/Description
12/01/2018	<ul style="list-style-type: none"> <li>• Revised conditions of coverage/special considerations language to indicate:               <ul style="list-style-type: none"> <li>○ Review by a Medical Director or their designee is required <b>only</b> for CPT codes 0071T, 0072T, 0404T, 37243, 58578, 58674, and 58999 in all sites of service</li> <li>○ For <b>participating providers in the office setting</b>: Precertification is required for CPT codes 0071T, 0072T, 0404T, 37243, 58578, 58674, and 58999 when performed in the office of a participating provider</li> <li>○ For <b>non-participating/out-of-network providers in the office setting</b>: Precertification is not required, but is encouraged for CPT codes 0071T, 0072T, 0404T, 37243, 58578, 58674, and 58999 for out-of-network services performed in the office; if precertification is not obtained, Oxford will review for out of network benefits and medical necessity after the service is rendered</li> </ul> </li> <li>• Archived previous policy version SURGERY 057.26 T2</li> </ul>