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New Treatment Options for Non-surgical Management of Uterine Fibroids

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Abstract

Purpose of review—Uterine fibroids are a common problem in reproductive age individuals frequently causing abnormal uterine bleeding, bulk symptoms, and adverse reproductive outcomes. Traditionally, almost half of the women with symptomatic fibroids received surgery for definitive treatment. There are a growing number of non-surgical options for treatment that became available for patients who desire conservative treatment or those with contraindications to surgery.

Recent findings—The introduction of oral gonadotropin-releasing hormone (GnRH) antagonists in combination with low dose physiologic hormonal therapy demonstrated improvement in heavy menstrual bleeding, pain, and quality of life with preservation of bone density, and modest reduction in uterine volume with few hypogonadal side effects. Magnetic resonance guided focused ultrasound surgery and uterine artery embolization continue to be minimally invasive procedural alternatives to hysterectomy that are safe and effective.

Summary—As more options for conservative management of uterine fibroids became available, it is important to counsel patients on possible options based on the size, location, number of the fibroids as well as severity of the symptoms, plans for pregnancy, how close they are to menopause and their treatment goals.

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Keywords

Uterine fibroid; uterine leiomyomas; GnRH antagonists; MRgFUS; UAE

INTRODUCTION

Uterine fibroids are a common problem in reproductive age individuals frequently causing heavy or prolonged menstrual bleeding, (AUB-L utilizing FIGO terminology), bulk symptoms, and adverse reproductive outcomes [1**]. Exact causes of uterine fibroid development are difficult to determine, however, risk factors include reproductive and endocrine factors such as estrogen and progesterone, increasing age up to menopause, nulliparity, early menarche, genetics, black or African-American race, and environmental toxicants [1**, 2*].

Traditionally, almost half of the women with symptomatic fibroids received either myomectomy or hysterectomy and fibroids have long been the leading cause of hysterectomy in the United States [3*]. Recently, a growing number of non-surgical options have become available for those who desire conservative treatment or those with contraindications to surgery. Currently available options are contraceptive steroid hormones, progesterone releasing intrauterine devices (IUD), tranexamic acid during menses (TXA), gonadotropin releasing hormone (GnRH) agonists and antagonists with and without additional hormones, and selective progesterone receptor modulator (SPRM). Similarly, interventions such as uterine artery embolization (UAE) and magnetic resonance guided focused ultrasound (MRgFUS) continue to be minimally invasive non-surgical alternatives available.

Many healthcare professionals including the American College of Obstetricians and Gynecologists (ACOG) support the use of conservative management before hysterectomy [1**, 2*]. However, a recent study revealed that overall, 59.7% of patients who underwent hysterectomy between 2011 and 2019 did not receive any conservative treatment before hysterectomy [4]. This chapter will review non-surgical management options for uterine fibroids, focusing more on newer treatment options.

Common symptoms requiring treatment

Most uterine fibroids are asymptomatic and are frequently found incidentally during annual exams. If asymptomatic, no evidence exists to support routine intervention. When symptomatic, common clinical presentations include heavy or prolonged menstrual bleeding (AUB-L), symptoms related to anemia, bulk related symptoms including pelvic pressure/pain, urinary incontinence or frequency, constipation, abdominal distension, and fertility issues including infertility or recurrent pregnancy loss and lastly, pregnancy complications including preterm delivery, fetal growth restrictions or fetal malpresentations. These symptoms are related to the size, location, and number of the uterine fibroids [1**, 2*].

Symptom-based approach to conservative treatment

Although fibroids are a common clinical problem worldwide, only a few randomized trials exist to guide treatment for uterine fibroids and there is no consensus on best treatment options [5]. Typically, for patients desiring pregnancy soon, treatment is aimed at optimizing the uterus for pregnancy and first tier treatments are mainly surgical removal of the uterine fibroids using hysteroscopy, laparoscopy, or laparotomy, but conservative management options should be discussed first based on her symptoms and treatment goals. For patients who do not desire fertility soon, management can be focused on control of symptoms rather than removal of fibroid themselves. Avoiding hysterectomy where appropriate is important given the increasing data of the long-term risks of hysterectomy even with ovarian conservation [6**].

Non-surgical management options for uterine fibroids

1. **Expectant management—**In general, patients without bothersome symptoms, no desire for intervention, and patients who are close to menopause are optimal candidates for expectant management. Although there is no evidence-based recommendation for the optimal time for evaluation, annual follow up with history and physical exam, imaging, and laboratory work up is reasonable. Patients should be counseled on active management options if they were to develop bothersome symptoms [1**].

2. **Medical management: Traditional options—**Most first line medical therapies can lessen AUB-L and pain, but don't lead to major changes in bulk symptoms. Thus, ideal candidates for all medical treatment include individuals with isolated HMB, without submucosal fibroid (FIGO type 0–1) who are ideal candidates for hysteroscopic myomectomy [6**]. Although contraceptive steroids (combined estrogen-progesterone contraceptives, progestin-releasing IUD) and tranexamic acid during menses are widely used, there are not good high quality studies demonstrating efficacy [1**]. However, there does appear to be a greater magnitude in the reduction of menstrual blood loss with the progestin-releasing IUD [1**].

   Second line agents including parenteral formulations of GnRH-agonists, and -antagonists reduce AUB-L and can also significantly impact bulk related symptoms but come with an increased risk of side effects that has limited therapy to 3–6 months. Thus, they are generally used to optimize future surgery or for perimenopausal women transitioning to menopause. Use of these agents before a planned surgery allows patients to have minimally invasive route for surgery, smaller incisions and improves preoperative anemia and perioperative outcomes [7]. While progesterone receptor modulators are also highly effective medical therapy, the hepatotoxicity seen with ulipristal acetate has made these agents unavailable for fibroid care in the United States and significantly limited their use elsewhere [8].

   Most medical treatment options are reversible, and regrowth of the fibroids is common between 3 to 9 months after the cessation of medication [9]. Mechanism of actions, advantages and disadvantages of each medical treatment options are described in table 1 [1**].

3. Oral gonadotropin releasing hormone (GnRH) antagonist combination therapy—Oral GnRH antagonist combination therapy (CT) are a new generation treatment option for uterine fibroids that maximizes suppression of symptoms and minimizes side effects. While the parenteral GnRH antagonists cetrorelix and ganirelix have long been used for controlled ovarian hyperstimulation for in vitro fertilization and the oral GnRH agonist elagolix as a single agent has been approved for the treatment of endometriosis and studied for fibroid treatment, all have significant hypogonadal symptoms [10]. The introduction of combination therapy utilizing early follicular phase levels of gonadal steroids (1mg estradiol and 0.5 mg norethindrone acetate) was pioneered for uterine fibroid treatment [11, 12]. Both elagolix (twice daily) and relugolix (daily) combination therapy are approved by US FDA for up to 24 months of use for management of AUB-L and the Relugolix CT is now approved for endometriosis treatment [10, 13, 14*].

Moreover, no clinical factor including uterine volume, baseline menstrual blood loss and the presence of concomitant adenomyosis has been shown to diminish the effectiveness of GnRH antagonist combination treatment [14*, 15, 16**]. The relugolix combination studies demonstrate treatment of other fibroid symptoms including substantial decreases in menstrual and non-menstrual pain, pelvic discomfort, and statistically significant reduction of uterine volume with mean volume reduction of about 10% [14*, 17**]. While similar data has not been published for elagolix combination, both are approved in the European Union (EU) for moderate to severe fibroid symptoms rather than AUB-L. Linzagolix is a third oral GnRH antagonist which is currently under investigation in the US. It is approved for fibroid treatment in EU using two doses (100mg vs 200mg) with and without the same hormonal combination as elagolix and relugolix combinations. Similar reduction in HMB was demonstrated with all four regimens, but uterine volume reduction was maximized when linzagolix was used without estradiol and norethindrone [18**]. The low dose of linzagolix appears to provide similar efficacy and safety to the combinations but can be used for patients unable or unwilling to take gonadal steroids.

The magnitude of AUB-L reduction was impressive with all three oral GnRH antagonist combinations (elagolix, relugolix, and linzagolix). Using alkaline-hematin extraction of menstrual products, responders had at least 50% reduction in AUB-L from baseline and reached a normal level of menstrual blood loss [12, 13, 14*, 18**]. Studies demonstrated induction of amenorrhea with longer duration of use in up to 64.6% of the patients treated with any of the oral GnRH antagonist combinations compared to the placebo group where amenorrhea ranged from 3.1 to 21.4% [12, 13, 14*, 18**]. Additionally, efficient correction of anemia was also noted in patients with baseline anemia [12, 13, 14*, 18**].

The safety profile of these agents is reassuring. Hot flashes were the most common adverse event in the clinical trials, but rates were close to that seen with placebo therapy [12, 13, 14*, 18**]. Both approved combinations carry a Black Box warning about the risk of thromboembolic disease, although no events were reported in the clinical trials, as a class warning utilized with all estrogen or progestin containing products.

Rare unplanned pregnancies were reported in these RCTs, and thus concomitant barrier contraception should be used with treatment [13, 18**, 19]. Uncomplicated live births have

been reported in some case reports, and no major congenital malformations attributed to oral GnRH antagonists were reported so far [18**, 20]. A trial is ongoing to examine if the relugolix combination provides contraceptive efficacy (NCT04756037, clinicaltrials.gov).

4. Non-invasive or minimally invasive interventions

a. Uterine artery embolization (UAE): UAE is a percutaneous angiographic procedure performed under fluoroscopy to control symptoms related to uterine fibroids [21]. It is a short procedure, typically about one hour long, performed while the patient is awake and done as a same-day procedure or with an overnight hospitalization. There are several different embolic agents used for UAE and no one material is reported to be superior to another in regards to clinical outcomes [22]. Following UAE, women typically have high rates of improvement in AUB-L and volume reduction with associated improvement in bulk symptoms which is maintained for up to 5 years [23].

Multiple randomized clinical trials have demonstrated the advantages of UAE compared to surgical fibroid treatments include not only improvement in symptoms but also markedly decreased risk of blood transfusion, shorter hospitalization, shorter procedure, and faster recovery times compared to surgeries [9, 24]. Ideal candidates for UAE should include all of the following: premenopausal, completed childbearing and symptomatic uterine fibroids [25]. High success rate in symptom control and improved quality of life have been reported in several studies in patients with AUB-L and pain [24, 25, 26, 27**]. However, in patients with isolated bulk related symptoms, the efficacy is more variable [24, 26, 27**]. While fibroids are immediately devascularized and can result in rapid diminution in bulk symptoms, true volume reduction takes place over time. In an RCT comparing UAE with myomectomy in patients who want to avoid hysterectomy, improvement in symptoms were noted in both groups at 2 years after the procedures, but the magnitude of improvement in quality of life was greater with myomectomy group at 4-year follow up [28**].

Following UAE, similar rates of major complications including unplanned hysterectomy, pulmonary embolism, and ovarian failure, compared to surgical management are reported, but higher rates of minor complications up to 21–64% including fever, chills, nausea, vomiting, pelvic infection, and pain related to postembolization syndrome are reported [1**, 23]. There may be some bias in this data since length of stay is usually shorter following UAE that a surgical procedure.

UAE can be recommended as an interventional procedure for the treatment of symptomatic uterine fibroids in patients who desire uterine preservation for future pregnancy. However, patients should be counselled about limited available high-quality data regarding future reproductive outcomes. In an RCT where they compared UAE vs myomectomy for pregnancy outcomes at 4-year point after the interventions, out of 98 women who underwent UAE, twelve reported pregnancies out of which seven resulted in live births, compared to five live births out of 105 women in myomectomy group [28**]. One meta-analysis including 227 pregnancies after UAE found increase in some adverse pregnancy outcomes like miscarriage, cesarean delivery, and postpartum hemorrhage, with no significant differences in preterm delivery and fetal growth restrictions [29]. However, in a more recent retrospective cohort study of 398 women who underwent UAE, increased rate of preterm

delivery with decreased rate of miscarriage was reported [30]. In this study, complete necrosis of the treated fibroids with restoration of uterine anatomy and ovarian protection were major predictive factors for clinical success [30]. Conflicting results exist regarding ovarian reserve testing, ranging from increased rates of ovarian failure to no differences before and after UAE. However, more recent studies suggest only transient decline in AMH and antral follicle counts up to 3 months after the procedure in younger patients less than 40 years of age [31]. Although there is growing evidence of UAE as an effective and safe modality for the treatment of uterine fibroids, and favorable fertility outcomes are reported, the use of UAE in women who wish to procreate requires careful counseling and shared decision making.

b. Magnetic Resonance guided Focused ultrasound (MRgFUS): Utilizing focused high intensity ultrasound energy with guidance using real-time diagnostic ultrasound (HIFU) or magnetic resonance (MRgFUS) to induce necrosis of fibroids by coagulation was first reported in 2003 [32]. Currently, only MRgFUS is approved by FDA for this indication since 2004 for the treatment of symptomatic uterine fibroids. This is generally an outpatient procedure using light sedation. While the patient is in supine position for HIFU and prone for MRgFUS, an individual fibroid is targeted and treated before moving on to other fibroids. Comparative effectiveness studies suggest that while there is improvement in quality of life and pain score following MRgFUS, the magnitude of improvement is less than that following UAE or myomectomy and the intervention rate subsequent to treatment is higher [33, 34*, 35, 36]. Interestingly, re-intervention was higher in younger patients with higher pre-treatment AMH levels [33]. When baseline MRI and follow up MRI was performed at 24 and 36 months after the procedures, reduction in fibroid volume was similar between MRgFUS and UAE groups [36].

However, MRgFUS is considered relatively safe procedure and has been shown to have fewer complications than surgical procedures [34, 37*]. Both types of focused ultrasound modalities may have a role in fibroid treatment when fertility optimization is the goal. A systematic review suggests reproductive outcomes are non-inferior to conventional fibroid treatments [38*]. Case series were reported regarding pregnancy outcomes in patients after treatment with MRgFUS and HIFU and demonstrated high term delivery rates with few pregnancy complications [39, 40]. Ovarian reserve after HIFU or MRgFUS as measured by hormonal levels before and after focused ultrasound treatment is also reassuring [34, 41*].

CONCLUSION

With the increasing prevalence of uterine fibroids and the number of women who delay childbearing, more patients will require uterine sparing treatment options for symptomatic uterine fibroids. Newer options include oral GnRH antagonist combinations for effective medical treatment and UAE and MRgFUS for minimally invasive procedures, with the evidence of improvement in AUB-L, quality of life, and reduction in the fibroid volume. As clinical presentations and personal treatment goals are variable, physicians should be able to discuss advantages and drawbacks of each treatment options in detail and treatment should be planned in an individualized manner based on shared decision making.

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KEY POINTS:

1. Conservative management of symptomatic uterine fibroids should be considered as initial treatment option.
2. Oral GnRH antagonist combinations demonstrated improvement in heavy menstrual bleeding, pain, and quality of life associated with uterine fibroids in addition to modest reduction in the uterine volume.
3. UAE and MRgFUS remain safe and effective alternatives to hysterectomy.

Table 1.

Summary of traditional medical treatment for symptomatic uterine fibroids

Class of agent	Mechanism of action	Advantages	Disadvantages	General Comments
Combined estrogen-progestin agents	Thinning of the endometrial lining, constant hormonal milieu	Reduces AUB-L and pain. Provides contraception. Additional health benefits: ovarian cancer/uterine cancer protection, reduction of anemia Inexpensive, widely available	Not effective for bulk related symptoms Not suitable for patients who cannot take high-dose estrogen	Available in oral pills, vaginal ring, transdermal patch
Levonorgestrel-releasing-IUD	Induce endometrial decidualization and atrophy	Reduces AUB-L and pain Provides contraception Ideal for patients who cannot take estrogen	Not suitable for FIGO type 1–2 uterine fibroids due to risk of IUD expulsion. Procedure required for insertion. Expensive in most environments	
Tranexamic acid	Prevent fibrin degradation	Reduces AUB-L Ideal for patients who cannot use hormonal agent. Only taken during menses on heavy days	Can only be used for up to 5 days a month	Given during heavy days of period at 1.3g dose three times daily
SPRM : ulipristal, mifepristone	Progesterone antagonism	Reduction in HMB and some volume reduction	Varied outcomes with pain Does not provide contraception. Rare cases of severe liver toxicity with ulipristal	Not available in the US for fibroid treatment
Parenteral GnRH agonists: goserelin, nafarelin, buserelin, leuprorelin	Interferes with pulsatile release of GnRH with reduced LH/FSH secretion, downregulation of GnRH receptor, and reversible hypogonadism	Reduce fibroid and uterine size and AUB-L. Used for 3–6 months before surgery to allow minimally invasive route for surgery, smaller incisions, improves preoperative anemia and perioperative outcomes	Initial flare effect Hypoestrogenic side effects Only short-term use: 6 months without ABT or 12 months with ABT Only in injectable forms Expensive Does not provide contraception	Available in 1- or 3-months depot
Oral GnRH antagonists: elagolix, relugolix, linzagolix	Competitive binding of the synthetic analog of endogenous GnRH to the receptors with reduced LH/FSH secretion, rapid HPO axis suppression, and reversible hypogonadism	Available in oral forms No initial flare effect. FDA and EU approved for 24 months of use for relugolix and elagolix when combined with 1 mg estradiol and 0.5 mg norethindrone acetate	Well tolerated with less hypoestrogenic side effects Expensive Does not provide contraception	Linzagolix is approved in the EU both with and without ABT.

Abbreviations: AUB-L, Abnormal uterine bleeding due to leiomyomas; LNG-IUD, levonorgestrel-releasing intrauterine device; SPRM, selective progesterone receptor modulator; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; ABT, add-back therapy