

# Current Medical Therapy for Uterine Leiomyomas

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Uterine leiomyomas are benign tumors arising from the myometrium and largely prevalent in the woman's reproductive years. The majority of women with leiomyomas either remain asymptomatic or develop symptoms gradually over time. When patients are symptomatic, the nature of their complaints is often attributable to the number, size, and/or location of their fibroids. Depending on a patient's symptomatology and reproductive plans, treatment options include expectant management, medical management (hormonal and non-hormonal), or surgical management (myomectomy or hysterectomy).

**Key Words:** Medical therapy, Uterine leiomyomas

## PRINCIPLE OF TREATMENT

The management of uterine leiomyomas varies significantly depending on the patient's age, symptoms, and reproductive plans. Appropriate selection of medical management (hormonal vs. nonhormonal) is necessary and will vary based on the patient's medical history, symptomatology, and goals for treatment. Treatment should satisfy three purposes: relief of signs and symptoms, sustained reduction of fibroid size, and maintenance or improvement of fertility, while minimizing side effects. Because of their benign nature, the most conservative therapeutic choice should be considered in order to minimize morbidity and/or side effects, while optimizing the patient's outcome.<sup>1</sup>

## HORMONAL MEDICAL MANAGEMENT

### 1. COMBINATION ORAL CONTRACEPTIVE PILLS

To date, combination oral contraceptives (COCs) are one of the most commonly prescribed therapies in the management of women with abnormal uterine bleeding, despite their limited efficacy in the management of leiomyoma-related uterine bleeding. As leiomyoma growth is stimulated by both estrogens and progestins, COC use should not be expected to provide symptomatic relief in terms of reducing the leiomyoma volume. In the short term, COCs can be used to improve heavy menstrual bleeding associated with fibroids, primarily through their suppressive effects on endometrial proliferation, but overall they

have no effect on decreasing leiomyoma volume or uterine size.<sup>2</sup> The advantages of COCs are the ease of accessibility, oral administration, low cost, and minimal side-effect profile. However, generally, COCs are not recommended for the treatment of abnormal uterine bleeding or bulk symptoms associated with leiomyomas, and patients should be offered alternative therapies for symptomatic relief.<sup>2</sup>

## **2. GONADOTROPIN-RELEASING HORMONE (GnRH) AGONIST**

GnRH agonists were one of the first medical therapies to be used in the treatment of leiomyomas. In 1999, the FDA approved the short-term use of leuprolide acetate as a pre-operative adjunct in women with symptomatic leiomyomas.<sup>3</sup> Treatment with GnRH-a decreases uterine volume, fibroid volume, and bleeding. However, the benefits of GnRH-a are limited by side effects and risks associated with long term use. High doses are associated with hypoestrogenism, leading to decreased bone mineral density.<sup>4,5</sup> A follow-up study examined the efficacy of short-term therapy in symptomatic women already scheduled for surgery, and demonstrated that such a protocol resulted a significant reduction in the rate of menorrhagia. Broekmans et al. treated a cohort of women with standard-dose triptorelin therapy for 8 weeks and saw a reduction in the myoma volume, similar to previous studies. They then randomized the women to receive varying doses for a maintenance course. The

investigators discovered that maintenance therapy with a low dose achieved similar reductions in volume as did treatment with a high dose, without a reduction in bone mineral density.<sup>6,7</sup>

## **3. GONADOTROPIN-RELEASING HORMONE (GnRH) ANTAGONIST**

GnRH antagonists act immediately to suppress the secretion of FSH and LH by blocking pituitary GnRH receptors.<sup>8</sup> The subsequent reduction in estradiol levels leads to improvement in bleeding patterns and reduction in leiomyoma size as early as 3 weeks after initiation of treatment. For example, the daily administration of ganirelix 2 mg in premenopausal women was associated with a 42.7% (14.1e77.0%) reduction in leiomyoma volume and 46.6% (6.1e78.6%) reduction in uterine volume over a median treatment duration of 19 days.<sup>9</sup>

## **4. LEVONORGESTREL INTRAUTERINE SYSTEM (LNG-IUS)**

In 2009, the FDA approved the LNG-IUS to treat heavy menstrual bleeding in women who opt for an intrauterine device for contraception. In women with fibroids, uterine size no larger than 12 weeks, and a normal uterine cavity, LNG-IUS substantially reduces menstrual bleeding.<sup>10</sup> The reduction in fibroid-related bleeding and symptoms has been reported in several studies. One observational study of 60 perimenopausal women with leiomyomas and excessive bleeding demonstrated that the LNG-IUS obviated the need for

hysterectomy in 89.5% of users. Nevertheless, some studies demonstrate little benefit in the treatment of fibroid-related symptoms. Mercurio et al. reported no improvement in leiomyoma symptomatology with the LNG-IUS, as well as an expulsion rate of 12%. Because of these conflicting studies, the LNG-IUS must be investigated further as a treatment modality for leiomyomas, and randomized controlled trials are needed to fully elucidate the benefits of the LNG-IUS, if any, on the symptoms and size reduction of leiomyomas. Once inserted, the LNG-IUS is effective for up to 5 years, thus potentially providing women with a long-term treatment option. Because it is not administered systemically, minimal side effects are reported, and patient compliance is not required after insertion, as there is no need for daily/monthly injections. However, given the increased risk of expulsion, the LNG-IUS is contraindicated in patients with severe uterine cavity distortion. Nevertheless, because of the notable reduction in bleeding, reinsertion of the LNG-IUS was requested by most women with symptomatic and large intramural leiomyoma who had a history of spontaneous expulsion.<sup>11,12</sup>

#### 4. GESTRINONE

Gestrinone is a synthetic steroid derived from ethinyl nortestosterone that has both anti-estrogenic and antiprogestogenic properties in the endometrium and other tissues containing estrogen and progesterone receptors.<sup>13</sup> A small number of studies have demonstrated reduction

in leiomyoma volume with the use of gestrinone. The proposed mechanism of action of gestrinone is via an antagonistic effect at estrogen and progesterone receptors, downregulating the activity of multiple genes regulating growth and proliferation, resulting in reduced fibroid size.<sup>14</sup>

#### 5. AROMATASE INHIBITORS

Aromatase inhibitors block estrogen synthesis by inhibiting or inactivating the microsomal cytochrome p450 enzyme aromatase, which catalyzes the synthesis of estrogens from androgens via hydroxylation.<sup>15</sup> The reduction in estrogen synthesis is detectable within 1 day of treatment, and aromatase is inhibited not only at the level of the ovary but also peripherally. Aromatase mRNA has been detected in 90% of fibroids, but not in normal myometrial tissue, which may explain how aromatase inhibitors act to suppress leiomyoma growth. It has been demonstrated that African American women have a higher prevalence of leiomyomas, and that the leiomyomas of African American women have higher aromatase expression than those of Caucasian or Japanese women. Thus, compared to other races, African American women may be more responsive to aromatase inhibitors, making this class of medications a beneficial target therapy.<sup>16</sup>

#### 6. SELECTIVE ESTROGEN RECEPTOR MODULATORS(SERMs)

Selective estrogen receptor modulators (SERMs) are nonsteroidal estrogen receptor (ER) ligands

that display tissue-specific ER agonist and/or antagonist estrogenic actions via tissue-specific alterations in gene expression. These medications are most commonly used for the treatment of ER-positive breast carcinoma. Two of the most commonly studied SERMs in the treatment of leiomyomas include tamoxifen and raloxifene.<sup>17,18</sup>

Tamoxifen is a partial ER agonist in bone, cardiovascular tissue, and the endometrium, but it has antagonistic effects in the breast and within the central nervous system. One small randomized, blinded controlled trial compared tamoxifen 20 mg daily versus placebo in women with symptomatic leiomyomas. Patients were treated for a 6-month duration, and those receiving tamoxifen showed a significant improvement in menstrual blood loss but no improvement in fibroid size or uterine volume. The study subjects reported many side effects, including hot flashes, dizziness, and benign endometrial thickening. Endometrial thickening occurs due to the ER agonist effect of tamoxifen on the endometrium, which places patients at an increased risk of endometrial hyperplasia and malignancy if used in the long term. Therefore, the negative side effects outweigh the marginal benefits of tamoxifen therapy, and its use is not recommended for the treatment of symptomatic leiomyomas.<sup>19</sup>

## 7. SELECTIVE PROGESTERONE RECEPTOR MODULATORS

Selective progesterone receptor modulators (SPRMs) have tissue-specific effects at progester-

one receptors (PRs), and they can either have a complete PR agonist or antagonist profile or have a mixed agonist/antagonist profile.<sup>20</sup> These agents have emerged as a promising therapy for the management of uterine leiomyomas, given the important role of progesterone in the promotion of leiomyoma growth. In vitro studies demonstrate that progesterone stimulates proliferative activity in cultured leiomyoma cells, but not in normal myometrial cells. Thus, by altering progesterone receptor signaling, SPRMs inhibit leiomyoma cellular proliferation and stimulate the apoptosis of leiomyoma cells without affecting normal myometrial cells. In addition, in vitro studies have shown that SPRMs increase alkaline phosphatase activity, upregulate cleaved caspase-3, and downregulate Bcl-2 in leiomyoma cells, thereby decreasing cellular proliferation and increasing apoptosis. SPRMs also induce the suppression of neovascularization of cultured leiomyoma cells. SPRMs may be used for the management of leiomyomas in patients preoperatively or in those wanting to defer surgical management.<sup>21</sup>

## 8. MIFEPRISTONE (RU-486)

Mifepristone is a synthetic 19-norsteroid SPRM with primarily PR antagonist activity, and was one of the first SPRMs to be developed and commonly utilized. In addition, mifepristone has some anti-glucocorticoid activity, although this is typically only seen with doses exceeding 200 mg daily. Although mifepristone is most commonly recognized as RU-486, an antiprogesterone used as an

abortifacient, it also exhibits inhibitory effects on myoma growth. Murphy and colleagues were the first to use mifepristone as a therapeutic agent in the management of leiomyomas.<sup>22,23</sup>

### 9. ULIPRISTAL ACETATE (CDB-2914/VA2914)

Ulipristal acetate (UPA), a synthetic steroid derived from 19-norprogesterone, binds to PR-A and PR-B with high affinity and has tissue-specific antagonistic and partial agonist effects.<sup>24</sup> UPA is tissue selective, with preferential binding noted in the uterus, cervix, ovaries, and hypothalamus. In vitro studies have shown that it does not activate the proliferation of healthy uterine tissue, but rather inhibits leiomyoma growth by down-regulating VEGF, and IGF-1 expression. In cultured leiomyoma cells, UPA induces the expression of MMPs, proteolytic enzymes involved in tissue remodeling, and decreases the expression of tissue inhibitor of metalloproteinases (TIMPs). However, UPA does not affect MMP expression in cultured myometrial cells. In Europe and Canada, UPA is licensed for use in the form of 5 mg/day for 3 months for the preoperative management of symptomatic leiomyomas in reproductive-aged women. In contrast, in the United States, UPA is approved by the FDA for use only as an emergency contraceptive. UPA has been found to be effective in reducing fibroid volume, decreasing menstrual bleeding, inducing amenorrhea, and improving quality of life in many women with symptomatic fibroids, with overall minimal adverse effects.<sup>25</sup>

## NONHORMONAL MEDICAL MANAGEMENT

### 1. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND TRANEXAMIC ACID

Several studies have demonstrated that NSAIDs and tranexamic acid were effective in reducing menstrual blood loss. But, these drugs were not shown to be effective for the treatment of menorrhagia in women fibroids.<sup>26</sup>

In summary, a variety of medical therapies are now available for women with leiomyomas, although each therapy has its own advantages and disadvantages. Currently, GnRH analogs and UPA are the most effective medical therapies, with the most evidence to support their reduction of fibroid volume and symptomatic improvement in menstrual bleeding. However, these medications are only effective in the short term; therefore, their use is somewhat limited. Additional forms of medical management are under investigation and may offer promising therapeutic options in the future. Ultimately, the treatment of leiomyomas must be tailored to the patient's personal treatment goals.

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### **Peer Reviewer's Commentary**

The management of uterine leiomyomas varies significantly depending on the patient's age, symptoms, and reproductive plans. The authors suggest several conservative therapeutic option such as hormonal and non-hormonal medical management. The most conservative therapeutic choice should be considered in order to minimize morbidity and/or side effects, while optimizing the patient's outcome.

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