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Issue 30.5: Hormones and uterine fibroids: from mechanisms to treatment

Role of Medical Management for Uterine Leiomyomas

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Abstract

Uterine leiomyomas, or fibroids, are the most commonly reported benign tumors of fertile women, affecting up to 70% of women of reproductive age. The majority of women with leiomyomas either remain asymptomatic or develop symptoms gradually over time. When patients are symptomatic, the nature of their complaints are often attributable to number, size and/or location of their fibroids. Bulky fibroids cause symptoms as a result of pressure on adjacent organs, such as the bladder, bowel or ureters. These symptoms may include pelvic pain and pressure, dysmenorrhea, dyspareunia, incontinence or constipation. In contrast, submucosal leiomyomas are more likely to cause abnormal uterine bleeding and impaired fertility. In the United States, it is estimated that the total economic impact related to fibroids is between 6 and 34 billion dollars, which includes the direct costs of health care as well as the indirect costs due to lost wages, disability and obstetric complications.

Key words: fibroids, uterine leiomyomas, abnormal uterine bleeding, medical management

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<A> Goals of Treatment

The management of uterine leiomyomas varies significantly depending on a patient's age, symptoms, and reproductive plans. Although rare, rapidly enlarging leiomyomas or those with abnormal features on ultrasound or MRI warrant surgical management and gynaecologic oncology consultation to rule out malignancy, such as leiomyosarcoma. For the majority of patients, however, surgery is considered elective, and plans for surgery will be dependent on each patient's preferences [1]. Many women opt to defer surgical management, and in others surgical management is contraindicated or considered high risk. Therefore, appropriate selection of medical management (hormonal versus non-hormonal) is necessary and will vary based on the patient's medical history, symptomatology and goals for treatment [2], [3]. 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 [4], [5]. 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. In patients with asymptomatic leiomyomas or those with minimal symptoms who do not desire future fertility, intervention can be delayed as long as close and appropriate follow up is ensured. At this time, there is insufficient evidence to support medical or surgical treatment of fibroids in asymptomatic patients [6]. Medical management may be particularly useful in cases of peri-menopausal women since they are unlikely to develop new symptoms and their fibroids will likely regress after menopause due to the lack of hormonal stimuli [7]. Furthermore, medical management is appropriate for patients with

multiple medical comorbidities in whom surgical intervention is generally contraindicated.

The first consideration before undertaking any therapy should be the determination of whether a patient wishes to conceive. In modern times, many women choose to postpone their first pregnancy to the later part of their reproductive years, and so the request for uterine preservation to maintain fertility is becoming more and more relevant in the gynaecologist's daily practice. Despite the development of new medical therapies for the reduction of fibroid size and alleviation of symptoms, impaired fertility remains an indication for myomectomy, while hysterectomy, ether total or subtotal, remains the best option for those symptomatic patients who do not desire future fertility and prefer definitive treatment.

Medical therapy may also play a role as a temporizing measure for symptomatic women approaching menopause who wish to avoid surgical intervention. For women requiring surgery, medical therapy may be utilized pre-operatively to minimize bleeding and thereby improve preoperative haemoglobin levels, or to decrease leiomyoma size in preparation for a minimally invasive surgical approach. Excessive menstrual blood loss is the leading cause of anaemia in the premenopausal period and patients with fibroids may have a prolonged history of heavy bleeding [8] and may be significantly anaemic. Normalization of haemoglobin levels pre-operatively is imperative to minimize the morbidity associated with intraoperative and/or postoperative blood transfusions [9]. This can be achieved through oral iron therapy, such as ferrous sulfate 325 mg twice or three times per day [8]. In those that cannot tolerate oral administration, parental therapy is an alternative to help restore the body's iron stores [8]. Both oral and parental iron

supplementation have been shown to improve anaemia and once the anaemia is corrected, the administration should be continued for at least 3 months. To aid in decreasing blood loss and improving anaemia, GnRH agonists can be given pre-operative to improve pre-operative haemoglobin levels, however, one potential negative effect is the reported softening of myomas that may cause more difficult cleavage of the myoma from the pseudocapsule during surgery [10], [11].

<A> Generalities of medical management

The medical management of leiomyomas should aim to improve a patient's quality of life by reducing signs and symptoms, while also minimizing side effects. Medical treatment may be preferred over a surgical approach, especially in patients who would like to avoid risks inherent to surgery or who desire uterine preservation. However, the adverse effects associated with prolonged medical therapies limit the duration of their use. In addition, a rebound increase in size of the leiomyomas can be noted after discontinuing hormonal medical therapy [12].

Hormonal: The widely accepted concept that the ovarian steroid hormones estradiol and progesterone support leiomyoma growth was initially proposed because of their frequency during the reproductive years, growth during pregnancy and regression after menopause. A number of subsequent *in vitro* and *in vivo* studies demonstrated the role of ovarian steroid hormones in promotion of leiomyoma cell proliferation [13], [14], [15], [16], providing rationale for the use of medical therapies such as GnRH agonists to reduce circulating steroid hormone levels, induce a so-called "pseudomenopause state," and thereby reduce fibroid size [17]. A recent study demonstrated a pivotal role of

progesterone in stimulating the growth of smooth muscle cells and the deposit of the extracellular matrix (ECM), opening new therapeutic implications for the use of antiprogestins [18], [19].

Non-hormonal: The role of excessive growth of a disorganized ECM in contributing to fibroid symptomatology has transformed the ECM as a novel target for medical treatment, and therapies aimed to reduce the deposit of collagen have therefore been developed [20]. There are non-hormonal medications, such as pro-coagulating agents and non-steroidal anti-inflammatory drugs, that are aimed at controlling symptoms of abnormal uterine bleeding and pain, but have marginal effects on fibroid growth or size [21], [22].

<A> Hormonal Medical Management

The rationale for the utilization of hormonal medical management stems from research demonstrating the increased expression of estrogen and progesterone receptors in leiomyoma cells relative to normal myometrium [23], [24], [25], [13]. Moreover, studies have demonstrated that the ovarian steroids estradiol and progesterone stimulate leiomyoma growth [13], [14], [15], [16]. This has led to the advent of various forms of hormonal medical management to block the stimulatory effects of ovarian steroids, decrease fibroid growth and alleviate symptoms in women with leiomyomas. Some patients may benefit from preoperative hormonal medical management to reduce fibroid size or uterine volume, increase pre-operative haemoglobin levels, and control bleeding [1], [23], [26]. Often, hormonal medical management is utilized only in the short term since long-term use is associated with minimal additional benefit and increased risk of

adverse events, such as osteoporosis [23]. In this section, we will focus on the available hormonal treatment modalities for uterine leiomyoma.

a) **<B> Combination oral contraceptive pills (COCs)**

To date, COCs are one of the most commonly prescribed therapies in the management of women with abnormal uterine bleeding, but have limited efficacy in the management of leiomyoma-related uterine bleeding. Since leiomyoma growth is stimulated by both estrogens and progestins [13], [15], [16], COC use should not be expected to provide symptomatic relief in terms reduction of leiomyoma volume. In the short term, COCs can be used to improve heavy menstrual bleeding associated with fibroids [6], primarily through their suppressive effects on the endometrial proliferation, but overall have no influence in decreasing leiomyoma volume or uterine size [27], [28]. The advantages of COCs are the ease of accessibility, oral administration, low cost, and minimal side effect profile [5]. 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, such as abnormal bleeding or pain.

b) **<B> Gonadotropin Releasing Hormone (GnRH) Agonists**

GnRH agonists were one of the first medical therapies utilized for the treatment of leiomyomas. In 1999, the FDA approved leuprolide acetate for short-term use as a pre-operative adjunct in women with symptomatic leiomyomas [26]. GnRH agonists are synthetic peptides that are structurally related to endogenous GnRH, however have longer

half-lives, greater receptor affinity, and greater potency through the alteration of the amino acids at the 6 or 10 positions [26], [29], [30]. Native GnRH is a decapeptide that is released from the hypothalamus in a pulsatile fashion.

i) *Mechanism of Action*: When GnRH agonists are administered in the follicular phase, an initial stimulation of follicle stimulating hormone (FSH) and luteinizing hormone (LH) release occurs, recognized as the flare effect. With continuous (as opposed to pulsatile) administration of GnRH agonists, down-regulation of pituitary GnRH receptors occurs, causing a decrease in the production of FSH and LH and subsequently of gonadal steroids [5], [29], [30]. This ultimately results in a hypoestrogenic state, which contributes to the pharmacologic efficacy of GnRH agonists [3], since leiomyoma growth is stimulated by estrogen. Several studies have demonstrated that tumor shrinkage may be directly proportional to the number of estrogen receptor (ER) positive cells [23], [13], [31]. In addition, GnRH agonists may have direct effects on leiomyomas by increasing matrix metalloproteinase (MMP) production, and decreasing the expression of veriscan [1], a chondroitin sulfate proteoglycan that is an important structure in the extracellular matrix (ECM), influencing tumor growth and proliferation [32]. Additional studies are underway to evaluate the application of local GnRH analogs, for example through an intrauterine system, since they appear to have some direct effects on uterine leiomyomas [1]. Previous studies have demonstrated the presence of GnRH receptor mRNA as well as GnRH-specific binding sites within leiomyoma cells, which supports a direct effect of GnRH agonists on leiomyoma regression [33], [34].

ii) Efficacy: GnRH agonists have been studied for the treatment of symptomatic leiomyomas for more than 25 years, and the therapeutic benefits are notable. Within the

first 3-6 months of treatment, most women have a 30-65% reduction in fibroid volume and significant improvement of their symptoms, while permitting the option for fertility preservation [5], [26], (21), (22), (23). A 2000 Cochrane systematic review evaluated 26 randomized controlled trials to determine the efficacy of GnRH agonists when used preoperatively before hysterectomy or myomectomy [35]. A significant reduction was noted in uterine volume, uterine gestational size, fibroid volume, and duration of hospital stay in those treated with GnRH agonists when compared with women treated with placebo, no therapy, or other medical therapy [23], [35], [36]. In addition, operative time for hysterectomy was significantly reduced, and those treated with GnRH agonists were more likely to undergo a minimally invasive approach to their hysterectomy (i.e., vaginal rather than an abdominal hysterectomy) [35]. Patients receiving GnRH agonists preoperatively also had significant improvements in pelvic symptoms and both pre- and post-operative haemoglobin levels [26], [35]. These authors concluded that GnRH agonist utilization for at least 3 months prior to surgery provides the benefits of reduction in uterine volume and fibroid size, controlled intraoperative bleeding, and the correction of pre-operative anaemia [14], [1], [35]. The usage of GnRH agonists seems to be more beneficial in cases of large myomas (>10 cm) if the myomectomy is to be performed laparoscopically and can help reduce operative time, intraoperative bleeding and risk of blood transfusion [37]. Furthermore, GnRH analogs may also be useful prior to hysteroscopic resection of submucosal myomas (G0-G1),, and one randomized controlled trial demonstrated that preoperative GnRH agonist use helped decrease operative times, fluid absorption, and the difficulty of the hysteroscopic procedure [38]. Perrone et al. [39] evaluated depot leuprolide acetate (11.25 mg every 90 days) for at least 6 months as an

alternative to surgery in premenopausal women greater than 45 years old. They reported similar efficacy between single and repeated dose, with a reduction in symptoms reported by 88% of patients receiving GnRH agonists, and no significant differences in self-reported sexual function [39].

ii) *Disadvantages/Side Effects*: The most commonly reported side effects of GnRH agonists are related to the hypoestrogenic state induced, the major limitation for long-term use, resulting in bothersome hot flushes, mood changes and vaginal dryness [5], [40]. In addition, the hypoestrogenic state leads to bone demineralization and over the long term can result in decreased bone mineral density (BMD) [14], [23], [41], [42], causing as much as a 5.5% reduction in BMD of the spine within the first 6 months of mono-therapy [43]. Moreover, treatment is associated with changes within the leiomyoma that may complicate surgical intervention. Leuprolide acetate treatment preoperatively can cause leiomyoma degeneration and obliteration of the cleavage plane between the myoma and the pseudocapsule, making the enucleation process and removal of fibroids difficult [31]. These myxoid changes may cause very small leiomyomas may to become too soft and difficult to visualize, and during myomectomy these leiomyomas may remain left behind. Other disadvantages to treatment include the relatively high cost of therapy and rapid regrowth of leiomyomas after the cessation of treatment [14], [41]. Multiple studies have demonstrated that after cessation of leuprolide acetate treatment, leiomyomas typically grow within 3 months, which further demonstrates the stimulatory role of estrogen on fibroid proliferation and growth [5], [26], [44], [13].

As a result of the profound hypoestrogenic side effects, long-term GnRH agonist therapy necessitates the use of hormonal add-back therapy to offset some of the hypoestrogenic symptoms and preserve bone mineral density [43]. Add-back agents must be selected appropriately to reduce side effects, improve compliance and allow prolonged therapy, while at the same time not compromising the benefits of GnRH agonist therapy [42]. Add-back therapy may include either the use of estrogens, progestins, or combined estrogens and progestins. An example of such add-back is the use of tibolone, a synthetic steroid with weak estrogenic and progestogen activity, in combination with GnRH agonists, which does not interfere with symptom improvement and provides similar reductions in fibroid volume [45], [46]. In a randomized, placebo controlled study, 75 women with symptomatic leiomyomas were administered either placebo or tibolone 2.5 mg, in combination with the GnRH agonist goserelin (3.6 mg subcutaneous implants monthly), for 3 or 6 months (30). Those receiving tibolone had better preservation of BMD (2% loss in spinal BMD, versus 5.5% loss in the placebo group $p<0.001$), and equivalent efficacy in reduction of leiomyoma size and leiomyoma-related symptoms [43].

c) <B> Gonadotropin Releasing Hormone (GnRH) Antagonists

First and second generation GnRH antagonists have been available for over 25 years, but their use was greatly limited because of their severe side effect profile (histamine release and allergic reactions). The advent of third generation GnRH antagonists, with an improved side effect profile, allowed for their use in the treatment of women with symptomatic leiomyomas [47]. The antagonistic properties are created by substituting

one amino acid at either the 1, 2, 3, 6 or 8 positions in the original decapeptide GnRH [29], [30], causing GnRH antagonists to compete with endogenous GnRH for pituitary binding sites. GnRH antagonists act immediately to suppress FSH and LH secretion by blocking pituitary GnRH receptors [29], [47]. 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 [30] (21). Because of its rapid onset of action, and avoidance of a gonadotropin flare phase, patients experience faster symptom relief [29], [13], [47]. Moreover, in women experiencing hypoestrogenic symptoms, discontinuation of the medication provides rapid improvement of side effects [13]. Multiple observational studies have demonstrated symptomatic improvement and reduction in uterine fibroid volume after GnRH antagonist therapy [29], [48]. For example, the daily administration of ganirelix 2mg in premenopausal women was associated with a 42.7% (14.1-77.0%) reduction of leiomyoma volume and 46.6% (6.1-78.6%) reduction of uterine volume over a median treatment duration of 19 days [29], [49]. This rapid reduction in fibroid volume was similarly demonstrated in another observational study that noted a 31% decrease in fibroid volume after 14 days of treatment, that was not accompanied by a flare-up in gonadotropin secretion [5]. Overall, the available evidence supporting the use of GnRH antagonists in the treatment of symptomatic fibroids is limited to observational studies and therefore, in the United States, cetrorelix and ganirelix (injectable GnRH antagonists) are rarely utilized in the treatment of fibroids. In addition, the cost GnRH antagonists is prohibitive, ranging from 15 to 25 thousand dollars per month [48], further limiting their use. The requirement for daily injections is another major limitation, since there are no available long acting

preparations [47], [48]. Since there are no significant additional benefits of GnRH antagonists when compared to GnRH agonists [30], and evidence supporting their use is limited, clinicians should generally not use these medications for the symptomatic treatment of uterine leiomyomas.

d) <B> Levonorgestrel- Intrauterine system (LNG-IUS)

In 2009, the FDA approved the LNG-IUS to treat heavy menstrual bleeding in women choosing an intrauterine device for contraception [26]. Although numerous studies indicate improvement in menstrual bleeding and haemoglobin levels when used in women with leiomyomas, they do not demonstrate an appreciable change in fibroid volumes, as measured by MRI and other imaging modalities [26], [23], [50], [51]. The reduction in fibroid-related bleeding and symptoms has been reported in several studies. One observational study of sixty perimenopausal women with leiomyomas and excessive bleeding demonstrated that the LNG-IUS obviated the need for hysterectomy in 89.5% of users [52]. Still, some studies demonstrate little benefit in the treatment of fibroid-related symptoms. Mercorio et al. reported no improvement of leiomyoma symptomatology with the LNG-IUS, as well as an expulsion rate of 12% [53]. Because of these conflicting studies the LNG-IUS as a treatment modality for leiomyoma needs further investigation [53], and randomized controlled trials are needed to fully elucidate the benefits of the LNG-IUS, if any, on leiomyoma symptoms and leiomyoma size reduction.

Once inserted, the LNG-IUS is effective for up to 5 years, thus potentially providing women with a long term treatment option [5]. Because it is not administered systemically, there are minimal reported side effects, and patient compliance is

eliminated once insertion is completed, since there is no need for daily/monthly injections [5]. However, given the increased risk of expulsion, the LNG-IUS is contraindicated in patients with severe uterine cavity distortion [5], [36], [42]. Nevertheless, because of the notable reduction in bleeding, re-insertion of the LNG-IUS was requested by most women with symptomatic and large intramural leiomyoma who had a history of spontaneous expulsion [51].

e) <B> Danazol

Danazol, an isoxazole derivative of 17α-ethinyl testosterone, causes a hypoestrogenic state and acts specifically at the level of the pituitary, ovary, and endometrium. It causes inhibition of pituitary gonadotropin secretion and ovarian steroid production, specifically resulting in low circulating estradiol levels, and a more androgenic hormonal milieu [36], [13]. When prescribed for the treatment of symptomatic uterine fibroids, danazol is administered at a dosage between 100-400 mg/day for a 4 to 6 month duration. In an observational study of 15 premenopausal women, danazol, at a dosage of 100 mg/day, reduced leiomyoma size by 37.6% ± 10%, and uterine volume by 29% ± 6.8% ($p<0.05$ for both), while improving haemoglobin concentrations and inducing endometrial atrophy [54]. The molecular mechanisms involved in altering and reducing fibroid size are not clear [42], [13]. Danazol is effective in the short-term but is overall less effective than GnRH agonists in the treatment of symptomatic leiomyomas. In addition, side effects are very common, which primarily include weight gain, muscle cramps, edema, hot flushes, hirsutism, headaches, depression, skin rash, acne and androgenic effects, such as deepening of the voice [29]. Because danazol is less effective than GnRH agonists, and

because of its many associated side effects, its use in women with symptomatic leiomyomas is generally discouraged.

f) <B> Gestrinone

Gestrinone is a synthetic steroid derived from ethinyl nortestosterone that has both antiestrogenic and antiprogestogenic properties in the endometrium and other tissues containing estrogen and progesterone receptors [29] [47], [55]. 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, down-regulating the activity of multiple genes regulating growth and proliferation, resulting in reduced fibroid size [56]. In a study of 24 women given gestrinone, all women reported suppression of menstruation by the end of the second month of treatment [57]. In another study of gestrinone, the benefits of treatment lasted 18 months following a 6-month treatment course [55]. The relatively slow reactivation of fibroid growth makes this treatment option appealing. An observational study in Italy demonstrated a 32% reduction in uterine volume in premenopausal women given gestrinone 2.5mg twice per week for 6 months as a treatment for their fibroids [55]. However, gestrinone has a similar side effect profile to danazol, and thus renders this medication intolerable for some. Reported side effects include weight gain, edema, decreased breast size, hirsutism, hot flushes, acne and headaches [29], [13], [47], [55]. Overall, the available studies evaluating gestrinone as a therapy for the management of uterine leiomyomas are few and limited to small numbers of patients, and thus this

medication is not recommended until more data is obtained via larger randomized controlled trials.

g) <B> 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 [26], [29], [50]. 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 [26], [23], [13]. Aromatase mRNA has been detected in 90% of fibroids, but not in normal myometrial tissue, and this may explain how aromatase inhibitors act to suppress leiomyoma growth [58]. 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 [58]. Thus, compared to other races, African American women may be more responsive to aromatase inhibitors, making this class of medications a beneficial target therapy [23], [58].

Two third-generation agents, letrozole (2.5mg daily) and anastrazole (1mg daily), have been studied for the treatment of symptomatic leiomyomas. The benefits of these third-generation agents are their rapid absorption [50]. Anastrazole does not appear to alter cortisol or aldosterone levels, and is not associated with androgenic or progestogenic effects [59]. In an observational study of 20 premenopausal women with symptomatic fibroids, Hilario et al. [59] demonstrated that administration of anastrazole (1mg/day) for 12 weeks resulted in up to a 32% reduction in fibroid size, as well as a reduction in

dysmenorrhea, menstrual blood loss, and duration of menses [59]. Anastrazole at this dosage was well tolerated, and there were no serious adverse effects [26], [59]. Another observational study of premenopausal women treated with letrozole 5 mg/day for 3 months demonstrated a 46.72% mean reduction of leiomyoma volume and a 21.67% mean reduction in uterine volume ($p<0.01$ for both) [60]. Menstrual blood loss was improved and no adverse effects on bone mineral density were seen [60]. However, 56% of women taking letrozole developed follicular cysts, most of which resolved shortly after treatment [60]. Because of this potential risk, some have recommended concomitant treatment with GnRH agonists (or antagonists), estrogen or progestins to prevent the increase in gonadotropin secretion [13]. Alternatively, a lower dose of letrozole (2.5mg/day) may be considered, and women treated with this dose for 3 months had no ovarian cyst formation, while still showing beneficial reductions in fibroid volume [13]. Another observational study of 30 symptomatic premenopausal women with at least one fibroid measuring 4 cm in size, given letrozole 2.5 mg/day for 12 weeks, noted a significant reduction in myoma volume and myoma size (5.4 ± 1.3cm to 4.3 ± 0.9 cm, $p<0.05$), and improved symptomatology, which persisted up to 3 months after treatment cessation [61].

To date there is one randomized trial comparing letrozole and the GnRH agonist triptorelin for 12 weeks of treatment in premenopausal women with symptomatic fibroids [62]. This study included a total of 70 patients, and after 12 weeks, those treated with letrozole had a 45.6% reduction in fibroid volume, not significantly different than the 33.2% reduction in the GnRH agonist group [62]. Although the individual studies all report an improvement in leiomyoma size and bleeding patterns with the use of

aromatase inhibitors [23], [62], a Cochrane review of one eligible study concluded that the evidence was still insufficient to fully support the use of aromatase inhibitors for women with symptomatic leiomyoma [50]. One limitation in their use is the frequent side effect of vasomotor symptoms owing to hypoestrogenism, although the proportion of women experiencing these symptoms is lower than in those taking GnRH agonists [62]. In addition, many other side effects of aromatase inhibitors limit their use, such as vaginal dryness, musculoskeletal pain, risk of bone demineralization with prolonged use, and ovarian cyst formation. The therapeutic benefits and adverse effects require further investigation with large-scale studies. At this time aromatase inhibitors are only used as an off label option for leiomyoma management [28].

h) <B> Somatostatin analogues

Since leiomyomas have higher expression of IGF-I and IGF-II receptors than normal myometrium [63], [64] somatostatin analogues, which inhibit pituitary growth hormone secretion, have been investigated as a treatment of leiomyomas [23]. Lanreotide is a long acting somatostatin analog available in depot form that has been shown to reduce growth hormone secretion [65]. A very small observational study evaluated the use of depot lanreotide (30mg every 14 days, for a 3 month duration) in seven women with leiomyomas, and noted a 41.6% reduction in mean leiomyoma volume and a 24% reduction in uterine volume after 3 months of therapy [65]. At this time, somatostatin analogues are still emerging as a potential new therapy for the management of leiomyoma. Additional studies are needed before any recommendations can be made

about their efficacy, safety and use as a treatment modality for women with symptomatic leiomyoma.

i) <B> Cabergoline

Cabergoline is a dopamine agonist that is most commonly prescribed for the treatment of hyperprolactinemia. The theoretical basis for its use in the medical management of leiomyoma lies in its dopaminergic inhibitory effect on secretion of GnRH, which should ultimately result in a reduction in GnRH and a mild hypoestrogenic state [29]. There are only a few small studies that have evaluated its efficacy in women with symptomatic leiomyomas. One study [66] demonstrated a reduction in leiomyoma size of approximately 50% after 6 weeks of use [66], which was comparable to the reduction in size seen with the GnRH agonist, diphereline [23]. Overall, cabergoline is well tolerated and has few adverse effects [29]. However, larger randomized controlled trials are warranted to better assess the potential use of this medication in the management of fibroids [47].

j) <B> Selective Estrogen Receptor Modulators (SERMs)

SERMs are non-steroidal 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 [23]. Two of the most commonly studied SERMs in the treatment of leiomyomas include tamoxifen and raloxifene.

Tamoxifen is a partial ER agonist in bone, cardiovascular tissue and the endometrium, but has antagonistic effects in the breast and within the central nervous system [13]. One small randomized, blinded controlled trial compared tamoxifen 20 mg daily versus placebo in women with symptomatic leiomyomas [67]. Patients were treated for a 6 month duration, and those receiving tamoxifen had a significant improvement in menstrual blood loss, but no improvement in fibroid size or uterine volume [67]. Study subjects reported many side effects, including hot flushes, dizziness and benign endometrial thickening. Endometrial thickening occurs due to tamoxifen's ER agonist effect on the endometrium, which places patients at increased risk for endometrial hyperplasia and malignancy if used long-term [13]. Therefore, the negative side effects outweigh the marginal benefits of tamoxifen therapy [13] [67], and tamoxifen use is not recommended for the treatment of symptomatic leiomyoma. No randomized controlled trials have been performed using tamoxifen because of the potential risk of endometrial hyperplasia and increased fibroid growth post cessation of therapy [23].

Raloxifene is second-generation SERM, with no agonist effects on the endometrium and only subtle antiestrogenic effects in mammary tissue. At this time there is no data to strongly support its use in the treatment of uterine fibroids [23]. A small randomized controlled trial of 25 premenopausal women treated with either raloxifene (180 mg/d) or no treatment for 3 months demonstrated only a 9.1%reduction in fibroid volume with raloxifene treatment, whereas a 13.1% increase in fibroid volume was noted after 3 months in the control group [68]. Of note, less than 10% of those in the treatment group complained of vasomotor symptoms, making raloxifene therapy more tolerable compared to tamoxifen [68]. This trial was limited in size,lacked the use of a placebo, demonstrated

no significant beneficial effect in reduction of fibroid volume, and thus cannot validate the use of raloxifene at this time. A Cochrane review which included 3 studies and a total of 215 participants, evaluating the use of raloxifene in the treatment of symptomatic leiomyoma, concluded that the effect of raloxifene effect on fibroid size and bleeding patterns is unclear and thus, larger controlled trials are still needed prior to recommending its use [13], [69].

k) <B> Selective Progesterone Receptor Modulators (SPRMs)

SPRMs have tissue-specific effects at progesterone receptors (PRs), and can be full PR agonists, antagonists, or have a mixed agonist/antagonist profile. 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 [70]. In vitro studies demonstrate that progesterone stimulates proliferative activity in cultured leiomyoma cells, but not in normal myometrial cells [51]. Thus, by altering progesterone receptor signaling, SPRMs inhibit leiomyoma cellular proliferation and stimulate apoptosis of leiomyoma cells without affecting normal myometrial cells [51], [70]. In addition, in vitro studies demonstrate that SPRMs increase alkaline phosphatase activity, upregulate cleaved caspase 3 and downregulate Bcl-2 in leiomyoma cells, thereby decreasing cellular proliferation and increasing apoptosis [26], [1], [71], [72], [25]. SPRMs also induce suppression of neovascularization of cultured leiomyoma cells [41], [25], [73]. SPRMs may be used for the management of leiomyomas in patients pre-operatively or in those wanting to defer surgical management [51], [70]. In the sections

below, we will discuss the commonly studied SPRMs, which have demonstrable antiproliferative, proapoptotic and antifibrotic actions on leiomyoma cells [13], [51]. Because SPRMs block progesterone action in the endometrium, concern exists about the development of endometrial hyperplasia in women taking these medications long-term [13]. Evaluation of specimens from women treated with SPRMs reveal changes in the endometrium that are benign in nature but necessitate the need of a new category for pathologic diagnosis, so that these changes can be appropriately classified [14], [23]. Progesterone receptor modulator endometrial changes (PAEC) include the histologic findings of endometrial glands lined by an incongruous epithelial cell type [74]. Glands may appear dilated or cystic, however the cells lack mitotic activity [13]. The histologic changes are reversible [13], [74], [75], reinforcing the concept that these changes are distinctly different from endometrial hyperplasia. An NIH-sponsored workshop was conducted to further discuss the topic of PAEC in women receiving various SPRMs [1]. After extensive review of many specimens, pathologists concluded that there was little evidence of mitosis, consistent with the antiproliferative effect of SPRMs. Furthermore, no specimens met criteria for endometrial hyperplasia, and changes seen were limited to PAEC [72]. Clinicians should be aware of these changes within the endometrium and follow these patients long term. Additional long-term follow up studies are necessary to fully define the outcomes associated with long-term use of these agents [23], [13].

i) <C> 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 [26], [13]. In

addition, mifepristone has some antiglucocorticoid activity, but these effects are usually only seen with doses exceeding 200mg daily [41], [13]. Although mifepristone is most commonly recognized as RU-486, an antiprogesterone used as an abortifacient, it also exhibits inhibitory effects on myoma growth [76]. Murphy and colleagues [77] were the first to utilize mifepristone as a therapeutic agent in the management of leiomyoma. In this observational study, the investigators administered mifepristone 50 mg/day, and demonstrated a 49.0 ± 9.2% reduction in uterine fibroid volume ($p < 0.001$ compared to pretreatment measurements), as well as significantly improved menstrual bleeding patterns, with all women reporting amenorrhea during the treatment period [77]. A follow-up prospective study by Murphy and colleagues demonstrated a similar reduction in fibroid volume but utilized lower dosages of mifepristone (5mg or 25 mg daily for 12 weeks) [78]. Since the initial studies evaluating mifepristone in women with symptomatic leiomyoma, additional prospective trials and randomized controlled trials have been conducted to further determine its efficacy as a therapeutic agent in these women. A randomized controlled trial performed in India compared mifepristone (10mg versus 25mg daily) for 3 months in women with symptomatic uterine fibroids [79]. Both dosages provided similar symptomatic relief with more than a 90% reduction in menstrual bleeding, but a greater reduction in myoma size was noted in the group receiving 25 mg of mifepristone when compared to the group receiving 10mg (35.7% versus 22.5% reduction, respectively, $p < 0.05$) [79]. The investigators concluded that mifepristone is a reasonable choice for the management of leiomyomas, since it also is cost effective and has minimal side effects [79].

Several systematic reviews have been conducted to assess the efficacy and safety of mifepristone in the treatment of symptomatic leiomyomas. Shen and colleagues conducted a meta-analysis of 11 randomized controlled trials, evaluating the use of mifepristone (dose range 2.5 mg to 25 mg/day for 3-6 months) in the treatment of symptomatic fibroids [80]. All dosages reduced fibroid volume and menstrual bleeding, without causing an increased risk of hyperplasia [80]. Another systematic review [81] of 6 trials demonstrated that daily treatment with mifepristone (5 to 50mg/day) for 3-6 months resulted in a 26-75% reduction in leiomyoma volume, and decreased the severity of dysmenorrhea, menorrhagia and pelvic pain [81]. However, side effects were present including hot flushes in approximately 38% of women, and endometrial hyperplasia in 28% (10/36) of the women screened by endometrial biopsy [28], [81]. The risk of hyperplasia raised safety concerns regarding the use of mifepristone. A subsequent 2012 Cochrane review of 3 randomized controlled trials evaluating mifepristone for the treatment of symptomatic fibroids demonstrated significantly reduced bleeding and improved quality of life in users of mifepristone, but no significant reduction in fibroid volume [82]. Mifepristone was therefore not recommended on the basis of this systematic review until better powered randomized controlled trials were conducted [82]. One study included in this review noted that 12/19 women in the mifepristone group developed endometrial hyperplasia after three months of therapy, versus 0/16 in the placebo group [83]. Prolonged use of mifepristone for greater than 6 months is associated with the development of progesterone receptor modulator associated endometrial changes (PAEC) [81], and therefore treatment-free intervals are recommended to decrease the risk of endometrial changes.

ii) <C> Asoprisnil (J-867)

Asoprisnil is a SPRM with a high degree of binding affinity for the progesterone receptor, moderate binding affinity for the glucocorticoid receptor, weak binding affinity for the androgen receptor, and no binding affinity for the estrogen or mineralocorticoid receptor [26]. Cultured leiomyoma cells express PR, with a predominance of PR-A compared to PR-B [84], and studies have demonstrated that asoprisnil increases the PR-A/PR-B ratio in cultured leiomyoma cells, without affecting normal myometrial cells [85]. The increased PR-A/PR-B ratio in response to asoprisnil correlates with a decreased concentration of vascular endothelial growth factor (VEGF) isoforms expressed in human leiomyoma cells, thereby decreasing myoma vascularization and growth [25], [85]. Asoprisnil has also been shown to suppress expression of other angiogenic factors, growth factors and receptors for VEGF and adrenomedullin in leiomyoma cells [25], [85]. This SPRM also induces apoptosis by activating the mitochondrial and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) pathways in leiomyomas [26], [25]. Furthermore, in in vitro studies, asoprisnil suppresses collage synthesis by stimulating ECM-remodeling enzymes specifically in cultured leiomyoma cells while preserving normal myometrial cells [26], [25].

A randomized controlled trial compared asoprisnil (5, 10 or 25 mg) versus placebo for 12 weeks in women with symptomatic leiomyomas [86]. All three doses were associated with a significant decrease in fibroid size, reduction in pressure symptoms, decreased menstrual bleeding and increased haemoglobin levels, and up to 80% experienced amenorrhea [86]. Treatment with asoprisnil was overall well tolerated, but approximately

10% of women reported vasomotor side effects, compared to 0% of women receiving placebo [86]. Vasomotor side effects associated with asoprisnil are generally minimal, because the medication does not induce a hypoestrogenic state; circulating estradiol concentrations remain in in the follicular phase range while on treatment with asoprisnil [87], [86]. Overall, there is a minimal side effect profile, and safety data has been reassuring but further details regarding asoprisnil's effects on bone mineral density, fertility, and recurrence rates of leiomyoma are still being investigated [41].

iii) <C> Telepristone (CDB-4124)

Telepristone is a potent antiprogestin with much less antiglucocorticoid activity than mifepristone [26]. Telepristone has selective in vitro activity, inhibiting the proliferation of leiomyoma smooth muscle cells and inducing apoptosis in these cells, without affecting the normal myometrial smooth muscle cells [88]. A randomized, double blinded placebo-controlled trial comparing 3 doses of telepristone (12.5, 25 or 50mg) with placebo or depot leuprolide acetate (3.75 mg IM every month) for a 3-month treatment duration demonstrated that 12.5 mg of telepristone reduced fibroid size by 17.9%, 25 mg of telepristone reduced fibroid size by 40.3%, and 50mg of telepristone reduced fibroid size by 40.3%. Depot leuprolide acetate decreased fibroid size by 32.6%, and the placebo group only decreased fibroid size by 10.6% [26], [89]. Although this study clearly demonstrates the utility of 25-50 mg telepristone in diminishing fibroid size, this was a very small study (30 women in total, with 5-6 patients included in each treatment arm) and the randomization scheme was not described. A recent phase 2 clinical trial using telepristone vaginal suppository in 4 dose formulations (3, 6, 12, or 24

mg) was conducted that demonstrated a favorable outcome when using telepristone 12mg/ day vaginally with a demonstrable shrinkage of fibroid size [90]. The efficacy and safety of telepristone warrants further study, specifically a placebo-controlled phase 3 trial.

iv) <C> Ulipristal acetate (CDB-2914/VA2914)

Ulipristal acetate (UPA), a synthetic steroid derived from 19-norprogesterone [26], binds the PR-A and PR-B with high affinity and has tissue-specific antagonistic and partial agonist effects [36], [72]. UPA is tissue selective, with preferential binding noted in the uterus, cervix, ovaries and hypothalamus [72]. In vitro studies demonstrate that it does not activate proliferation of healthy uterine tissue [5], [16], and inhibits leiomyoma growth by down-regulating VEGF, and IGF-1 expression [23], [72]. In cultured leiomyoma cells, UPA induces expression of MMPs, proteolytic enzymes involved in tissue remodeling, and decreases expression of tissue inhibitor of metalloproteinases (TIMPs) [72]. However, UPA does not affect MMP expression in cultured myometrial cells. [26], [72].

In Europe and Canada, UPA is licensed for use in the form of 5mg/day for 3 months for preoperative management of reproductive aged women with symptomatic leiomyomas [5], [28], [36], [72]. In the United States, UPA is approved by the FDA for use only as an emergency contraceptive, as Ella ®. UPA has demonstrated effectiveness 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 [14], [28].

Many clinical studies have evaluated the efficacy of UPA in the treatment of symptomatic leiomyomas, however the most widely cited studies investigating UPA include the European phase III studies, PGL4001 (UPA) Efficacy Assessment in Reduction of Symptoms Due to Uterine Leiomyomata (PEARL), which demonstrate UPA efficacy [91], [44], [75]. PEARL I compared UPA at 5 and 10 mg/day dosing with placebo for a 13 week treatment period [75]. Patients were assessed using the pictoral blood loss assessment chart (PBAC). Amenorrhea was reported by 73% of patients treated with 5mg of UPA and by 82% of patients receiving 10 mg of UPA, while amenorrhea was only noted in 6% of patients treated with placebo [75]. Furthermore, the majority of patients treated with UPA achieved amenorrhea within the first 10 days of treatment [75]. Overall, 92% of patients who received UPA reported improvement in uterine bleeding after 13 weeks of treatment, compared to only 19% of women receiving placebo. Fibroid volumes, as measured by MRI, were significantly decreased in women treated with UPA compared with placebo (21% reduction in size with 5mg of UPA, 12% reduction in size with 10mg of UPA, and 3% reduction in size with placebo, p=0.002) [75]. PEARL II was a double blinded, non-inferiority trial that included 307 patients randomly assigned to 5 or 10 mg of UPA versus a GnRH agonist, depot leuprolide acetate, for 3 months of use [91]. PBAC was used to assess menstrual blood loss, and reduction in uterine bleeding was comparable in all three groups, occurring in 98% of those receiving 10mg UPA, 90% for 5mg of UPA, and 89% for leuprolide acetate [91]. However, median time to achieve amenorrhea was significantly less in women given UPA (5-7 days) than in those given leuprolide acetate (21 days) [91]. Women receiving leuprolide acetate had a 47% reduction in uterine volume, compared with 20 and 22%

reduction in the 5mg, and 10mg UPA groups, respectively ($p < 0.05$) [91]. However, there were similar reductions in volume noted in the largest fibroids between these groups. Given the overall findings, the investigators concluded that both UPA doses (5 and 10 mg/day) were noninferior to depot leuprolide acetate (3.75 mg/month) in controlling uterine bleeding. The major benefit of UPA over leuprolide acetate is a less hypoestrogenic state, with significantly fewer vasomotor symptoms and hot flushes reported by women receiving UPA (10% versus 40% in the leuprolide acetate group, $p<0.001$) [91]. PEARL III was an extension trial that assessed efficacy and safety of long-term UPA treatment in women with symptomatic fibroids [44]. Patients were treated with UPA 10mg daily, followed by norethindrone acetate (NETA) 10 mg daily versus placebo for 10 days. Thereafter, patients could either leave the study or continue UPA 10mg (and NETA/placebo) for up to three 12-week courses [44]. In between each 12-week course, patients received no treatment and were required to have a full menses before receiving additional UPA treatment. By the end of the 4th treatment course, 89.7% of women experienced amenorrhea [44]. There was a 72.1% median reduction in uterine volume in women who completed four treatment courses, and at 3 months of follow-up after discontinuation of treatment, there was a 58.8% median reduction in leiomyoma size [44]. These results highlight the potential of UPA for long-term medical management of symptomatic uterine leiomyomas, which may allow some women to avoid surgery [5], [44]. In addition to the PEARL studies, a randomized, double blinded placebo-controlled trial in the United States evaluated UPA (10mg, 20mg or placebo) for 12 weeks of treatment [92]. Patients were also offered a second 12-week treatment period. There were no adverse events reported, and UPA was effective in significantly controlling

bleeding for 3-6 months, significantly reducing fibroid size, and improving overall quality of life [92].

Reported side effects of UPA treatment include headaches and breast tenderness [91], [44], [75], [92]. In addition, physiologic endometrial changes (PAEC) are possible. As noted earlier, these are considered benign, consist of cystic glandular dilation, and to date have not been associated with an increased risk of endometrial hyperplasia or malignancy. Clinicians and pathologists should be aware of these changes in order to avoid misclassifying as hyperplasia. However, these patients require long term follow-up since premalignant changes may take years to develop. Long-term studies are necessary to evaluate such outcomes.

Clearly, UPA appears to have many advantages. It is an oral medication well tolerated by most, and is highly effective in the treatment of symptomatic leiomyomas, not only in reducing menstrual bleeding related symptoms, but also in decreasing fibroid, uterine volume and improving overall quality of life. The effects of fibroid volume reduction after treatment discontinuation also appear to be more prolonged with UPA than with GnRH agonists [44]. In distinct contrast to leuprolide acetate, hypoestrogenic side effects in women treated with UPA, if any, are minimal, since circulating estradiol levels are maintained in the mid-follicular range throughout treatment duration [5], [14], [23]. This improves patient satisfaction and compliance [14]. Moreover, there is minimal associated loss of bone mineral density. In addition, the time to achieve UPA's therapeutic effects is relatively quick relative to leuprolide acetate, given that leuprolide acetate initially has a gonadotropin "flare" effect when administered in the early follicular phase, prior to induction of a hypoestrogenic state [5]. Based on these advantages, UPA

may be the preferred choice for preoperative adjuvant therapy in women with symptomatic leiomyomas.

Overall, a variety of reasonable choices exist for the medical management of symptomatic leiomyoma, and decision-making will depend largely on degree of symptomatology and overall goals for therapy (i.e. short-term/preoperative versus long-term). Surgical management, while usually elective, remains the only definitive therapy for symptomatic leiomyomas. This section has discussed the available hormonal options that are both currently in use in Europe and the United States, as well as others that are still under investigation, such as aromatase inhibitors, newer SPRMs, gestrinone, and somatostatin analogues. Both UPA and leuprolide acetate are appropriate choices for the relief of pressure symptoms and abnormal uterine bleeding, however UPA offers the advantages of oral availability, rapid onset of action, and minimal vasomotor symptoms. The major disadvantage of UPA is the outstanding concern of the long-term effects of UPA on the endometrium. Thus, patients should be counseled about available options and treatment should be based on goals for therapy.

<A> Non-Hormonal Medical Management

a) <B> Tranexamic acid

Tranexamic acid is a synthetic lysine derivate that prevents fibrin degradation through a reversible block of the lysine binding site on plasminogen. Tranexamic acid was approved by the FDA in 2009, and is accepted worldwide for the treatment of heavy menstrual bleeding in women with and without fibroids [13], [21].

Mechanisms of action: The leading cause of heavy menstrual bleeding in patients affected by leiomyomas is a change in the venous structures of the myometrium and endometrium, where the presence of fibroids can cause venule ectasia [93]. There is a subsequent venous compression by the fibroid and local release of vasoactive growth factors into the blood supply. Moreover, because of the increase in the caliber of the vessels, there is a resultant decrease in the normal haemostatic actions of platelets and other coagulation factors [94]. Tranexamic acid is efficacious under these circumstances because it has antifibrinolytic effects. It competitively inhibits the activation of plasminogen to plasmin, which subsequently inhibits endometrial plasminogen activator [95]. The effect is decreased fibrinolysis and clot breakdown, and thus overall decreased menstrual blood loss.

Efficacy: Despite the effectiveness of oral administration, the vast majority of pharmacokinetic studies of tranexamic acid in women with menorrhagia have been conducted with intravenous administration. When administered orally to healthy male volunteers, tranexamic acid has a half-life of 2 hours, and 40 to 70% is excreted unchanged in the urine within 24 hours [96]. The antifibrinolytic activity of the drug in patients affected by menorrhagia is higher when compared to those with normal cycles and this may be due to endometrium-derived plasmin and plasminogen activators [97]. The oral administration of 2-4 g/day for 4-7 days per cycle has been reported to cause a 34-59% reduction in menstrual blood loos, with a mean reduction of 75 ml of menstrual blood loss per cycle [98]. The recommended dosage varies by country but is generally recommended at a dosage of 1 to 1.5 grams three times per days for 3-4 days. In addition to its procoagulative effects, tranexamic acid has been demonstrated to cause ischemic

necrosis of the fibroid with subsequent reduction in size due to thrombosis of the vessels [95].

Contraindications and side effects: Tranexamic acid is generally well tolerated, and the risk of venous thromboembolism is not increased in those treated, as it does not interfere with other coagulation factors. The more commonly reported side effects are gastrointestinal complaints, such as nausea, vomiting or diarrhea, which were reported in up to 12% of patients. Another frequently experienced symptom is dysmenorrhea that may be attributable to the development of necrosis within the myoma. If necrosis occurs, patients may develop symptoms similar to those occurring after uterine artery embolization which include pelvic pain, nausea, malaise, and low-grade fevers [99].

b) <B> Non-steroidal anti-inflammatory drugs

Several studies have demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) are effective in reducing menstrual blood loss. NSAIDs reduce prostaglandin synthesis at the level of the endometrium by inhibiting cyclooxygenase. Endometrial prostaglandin receptors may play a role in developing aberrant vascularization and promoting neoangiogenesis, which can result in abnormal uterine bleeding [100]. Thus, the inhibition of prostaglandin synthesis aids in reducing menstrual bleeding.

Efficacy: A recent Cochrane review including 18 randomized controlled trials reported NSAIDs as superior to placebo or comparable to other medical treatments [22]. In patients treated with NSAIDs, there was a 30% reduction of menstrual blood loss [22]. This class of drugs appears to be effective only for symptom relief, without affecting fibroid size. However, NSAIDs may also be beneficial in controlling anaemia and pain

associated with menses. There are no reported differences in the effectiveness of different types of NSAIDs [101]. NSAIDs are considered an appropriate first-line medication for heavy menstrual bleeding, while also alleviating dysmenorrhea. They may also serve as an alternative in case hormones are not well tolerated by the patient [101].

<A> Emerging Therapies

a) <B> Vitamin D

Vitamin D is a steroid molecule group of fat-soluble prohormones with hormone-like effects. The active metabolite form of vitamin D is D_3 (cholecalciferol). Several animal studies have shown the widespread effects of cholecalciferol, including effects on the cardiovascular, immune and reproductive systems. Cross-sectional and observational studies in women with fibroids demonstrated that lower serum levels of Vitamin D, were inversely correlated with leiomyoma volume [102]. A larger series demonstrated that patients with fibroids are more likely than those without fibroids to have low levels of Vitamin D (25-hydroxyvitamin D [25(OH)D] <10 ng/mL) (OR 2.4, 95% CI 1.2- 4.9) and a case-control study showed a 32% lower risk of having fibroids in women with sufficient vitamin D levels (25(OH)D >20 ng/mL) when compared with insufficient Vitamin D levels [103], [104]. *In vitro* studies demonstrated that treatment of immortalized fibroid cells with vitamin D caused a reduction in fibroid cell growth; this effect may be attributable to the interaction of vitamin D with nuclear antigens, leading to lower expression of proliferation and anti-apoptotic markers, and an antifibrolytic effect mediated by MMP and collagen expression [105], [106], [107], [108]. Compared to normal myometrium, leiomyomas have increased MMP activity, and vitamin D appears

to down-regulate MMPs, thus decreasing uterine fibroid pathogenesis [107]. Furthermore, an *in vivo* study using a rat model of fibroids, demonstrated a reduction of 75% of uterine tumor size after the administration of D_3 for 3 weeks [109]. Additional studies are needed to test the efficacy of Vitamin D supplementation in women in the treatment of leiomyomas.

b) <B> Growth factor modulators

Recent studies of human fibroids have demonstrated a population of somatic stem cells that are capable of self-renewal and proliferation in a hormone-dependent manner [110], [111]. The possibility of establishing a self-promoting loop may be linked to the interaction of fibroid with the surrounding myometrium through autocrine and paracrine mediated mechanisms via growth factors and cytokines [112]. The pivotal role of the surrounding myometrium has been demonstrated by the gene expression profile of the pseudocapsule that surrounds the fibroid [113], [114].

Pirfenidone is a pyridine molecule with proven antifibrotic effects in animal models through the inhibition of the transforming growth factor (TGF)-beta pathway that is strictly linked with the formation of the extracellular matrix [115]. *In vitro* studies of pirfenidone have demonstrated its efficacy in reducing myometrial/leiomyoma cell proliferation and decreasing the expression of the mRNA of collagen I and III in a dose-dependent manner without any cytotoxic effects [20]. This new medication is still undergoing phase III drug testing. Although it appears to have promising results for the treatment of the idiopathic pulmonary fibrosis and is under evaluation to treat myocardial

fibrosis, to date there have not been any human studies evaluating pirfenidone for treatment of leiomyomas [116], [117].

Other drugs that interact with TGF-beta (SB-525334), epidermal growth factor (AG1478, TKS050), vascular endothelial growth factor (Thiazolidinediones) or fibroblastic growth factor (Interferons) signaling have been studied in *in vitro* leiomyoma models with promising results. However, these agents have not yet been studied in humans for the treatment of leiomyomas, and significant side effects (as in the case of interferon alpha) will limit their application in the treatment of leiomyomas [118], [119].

c) <B> Gene therapy

During the last few decades, the use of an adenoviral vector to deliver genetic material to target cells has been investigated as a treatment option for cancers and other metabolic diseases. The localized nature of leiomyomas also makes them suitable for gene therapy. Studies using a rat model have demonstrated that adenoviral vectors are able to infect uterine leiomyoma cells and inhibit cell proliferation, increase apoptiosis, and cause regression of leiomyomas [120], [121], [122]. For example, *in vitro* studies utilizing intrafibroid delivery of a dominant-negative mutant estrogen receptor (Ad-DN-ER) [thus blocking the transcription of E-responsive genes and inactivating estrogen signaling] resulted in reduction of leiomyoma cell proliferation and increased apoptosis [120].

The transplantation of leiomyoma cells transfected by Ad-DN-ERs in mice showed smaller tumors in comparison to controls, and an additional injection of the adenovirus into the leiomyoma resulted in further shrinkage of the tumor [121].

Similarly, other vectors have been developed to deliver the herpes simplex virus thymidine kinase (HSV1TK) gene to target cells. When these transfected cells are treated with the guanosine analog ganciclovir, ganciclovir is phosphorylated by HSV1TK to form a toxic product that inhibits DNA synthesis, thereby causing cell death by apoptosis [123]. Studies using adenovirus-mediated delivery of HSV1TK in a rat model demonstrate that treatment with gancicicloviir inhibits leiomyoma cell proliferation, resulting in an increased number of apoptotic cells and the regression of uterine leiomyomas [122]. The feasibility of gene therapy for the treatment of leiomyomas is still under evaluation and human studies are lacking, but it may be a potential option in the future.

<A> Summary

Leiomyomas remain highly prevalent in reproductive aged women, and as women continue to delay childbearing, an increasing number will require fertility preserving treatment options. As a result, medical management of leiomyomas is of pivotal importance in providing patients with symptom relief and the opportunity to maintain fertility. A variety of medical therapies are now available for women with leiomyomas, although each have their own advantages and disadvantages. At this time, GnRH analogs and ulipristal acetate 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, and therefore their use is somewhat limited. Additional forms of medical management are under

investigation and may be promising therapeutic options in the future. Ultimately, treatment of leiomyomas must be tailored to the patient's personal treatment goals.

Practice points

- Although surgical management remains the only definitive therapy for symptomatic leiomyomas, a number of medical therapies are now available for the treatment of certain women who desire uterine preservation and who wish to avoid surgery.
- Appropriate selection of medical management will depend largely on degree of symptomatology and overall goals for therapy.
- GnRH agonists are efficacious in the management of abnormal uterine bleeding secondary to leiomyomas both pre-operatively as well as in perimenopausal women who wish to defer surgical management.
- Ulipristal acetate, a selective progesterone receptor modulator (SPRM), has emerged as an effective medication in decreasing menstrual blood loss and myoma size when used in the short term.
- Non-hormonal medications such as tranexamic acid and NSAIDs may also be beneficial in reducing menstrual blood loss related to fibroids.

Research agenda

Future investigative efforts should focus on determining:

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- Efficacy and safety of hormonal therapies such as aromatase inhibitors, gestrinone, somatostatin analogues, and newer SPRMs in the treatment of symptomatic leiomyomas
- Efficacy and safety of long-term use of ulipristal acetate and other SPRMs in the treatment of women with symptomatic leiomyomas, including long-term follow-up of endometrial changes after SPRM use
- Effects of Vitamin D supplementation on leiomyoma size and associated symptoms
- Efficacy and safety of growth factor modulators in the treatment of leiomyoma
- Further development of gene therapy targeted directly at decreasing leiomyoma size and reducing symptomatology

Conflict of interest

The authors report no conflicts of interest.

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Highlights

- Medical management should be considered as an alternative to surgery in the management of fibroids
- Selection of medical management should be based on a patient's symptoms
- GnRH agonists and Ulipristal acetate are effective in decreasing blood loss and fibroid size
- Non-hormonal medications may also be beneficial in reducing menstrual blood loss due to fibroids.

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