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Medical Treatment of Uterine Leiomyoma

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Abstract

Uterine leiomyomas (also called myomata or fibroids) are the most common gynecologic tumors in the United States. The prevalence of leiomyomas is at least 3 to 4 times higher among African American women than in white women. Pathologically, uterine leiomyomas are benign tumors that arise in any part of the uterus under the influence of local growth factors and sex hormones, such as estrogen and progesterone. These common tumors cause significant morbidity for women and they are considered to be the most common indication for hysterectomy in the world; they are also associated with a substantial economic impact on health care systems that amounts to approximately $2.2 billion/year in the United States alone. Uterine myomas cause several reproductive problems such as heavy or abnormal uterine bleeding, pelvic pressure, infertility, and several obstetrical complications including miscarriage and preterm labor. Surgery has traditionally been the gold standard for the treatment of uterine leiomyomas and has typically consisted of either hysterectomy or myomectomy. In recent years, a few clinical trials have evaluated the efficacy of orally administered medications for the management of leiomyoma-related symptoms. In the present review, we will discuss these promising medical treatments in further detail.

Keywords

leiomyoma, fibroid, myoma, nonsurgical treatment, medical

Uterine leiomyomas are the most common benign pelvic tumors in women.[1,2] They are monoclonal tumors of the smooth muscle cells of the myometrium and consist of large amounts of extracellular matrix that contains collagen, fibronectin, and proteoglycan.[2,3] A thin pseudocapsule that is composed of areolar tissue and compressed muscle fibers usually surrounds the tumors.[4] Leiomyomas may enlarge to cause significant distortion of the uterine surface or cavity. Although they are benign, they commonly result in severe symptoms, such as heavy, irregular, and prolonged menstrual bleeding as well as anemia. Uterine leiomyomas have also been associated with numerous other medical disorders, such as infertility, recurrent abortion, and preterm labor.[5] These clinical complications negatively impact women's health. Uterine leiomyomas are the most cited indication for more than 600 000 hysterectomies performed in the United States annually, and this major surgery is associated with morbidity and mortality as well as a huge economic impact on health care delivery systems that is estimated to be approximately $2.2 billion/year.[6]

Uterine Leiomyomas are More Common in African Americans

Weiss et al published (2009) a multiethnic, multicenter, community-based longitudinal cohort study of 3302 women between the ages 42 and 52 in which the authors surveyed the overall perceived health before and after hysterectomy in addition to the presenting symptoms. The results denote that leiomyomas do not affect the different races equally; African American (AA) women have leiomyoma-related symptoms more frequently than caucasian women (85% vs 63%; $P = .02$).[7] The increased prevalence of leiomyomas in dark-skinned races was already observed a long time ago. In a report that was published more than 115 years ago, leiomyomas were described as a disease that was considered to be specific to the dark-skinned races.[8] Dark-skinned women, such as AAs, also had higher numbers of leiomyomas and tended to have larger uteri, which in turn may explain the higher incidence of in-hospital complications or blood transfusion requirements in AA women compared to white women.[9,10] The overall incidence of uterine leiomyomas is estimated to be 3 to 4 times higher in AA women compared to caucasian women.[11-14] Recent data have also confirmed that the age-standardized rates of ultrasound- or hysterectomy-confirmed leiomyomas were

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significantly higher in black women compared to white women.[15] Baird et al[16] demonstrated that more than 80% of black women and nearly 70% of white women develop uterine leiomyomas. However, it is suggested that both black and white women in the United States develop uterine leiomyoma before approaching menopause and that the tumors develop at earlier ages in black women compared to white women. The ethnic differences in the incidence of uterine leiomyomas were reflected in the hysterectomy rates in the different ethnic groups. It was found that the annual age-adjusted hysterectomy rates were significantly higher in black women (65.4%) compared to white women (28.5%).[17] The racial disparity in the incidence of uterine leiomyomas persisted even after adjustment for factors such as marital status, body mass index, age at first birth, years since last birth, history of infertility, age at first oral contraceptive use, and current alcohol consumption.[18] The molecular mechanism underlying this ethnic disparity is not fully understood. Polymorphism of genes that are involved in estrogen synthesis and/or metabolism (*COMT*, *CYP17*), variations in the expression levels or function of estrogen and progesterone receptors or retinoic acid nuclear receptors (retinoid acid receptor-α, or retinoid X receptor-α), or the aberrant expression of micro-RNAs are some of the molecular mechanisms that may be involved.[10,19]

The Clinical Presentation of Uterine Leiomyomas

- Asymptomatic
- Abnormal uterine bleeding
  - Menorrhagia
  - Anemia
- Pelvic pressure
  - Urinary frequency
  - Urinary incontinence
  - Difficulty with urination
  - Hydronephrosis
  - Constipation
  - Tenesmus
- Pelvic mass
- Pelvic pain
- Infertility
- Obstetric complications
- Pregnancy related
  - Myoma growth
  - Red degeneration & pain
  - Spontaneous miscarriage
- Malignancy
- Rare associations
  - Ascites
  - Polycythemia
  - Familial syndromes, renal cell carcinoma
- Benign metastasizing

Diagnosis of Uterine Leiomyoma

- Pelvic examination: Enlarged, irregular, firm, non-tender ut.
- Ultrasound: Trans-vaginal ultrasound, if uterus <375 ml volume, <4 myomas in number well-defined, hypoechoic
- Saline sonohysterography: For submucous fibroids or polypi
- MRI: Best method for exact mapping, numbering of fibroids
- Hysteroscopy: Diagnosis of submucous fibroids

Current Treatment Options for Uterine Leiomyomas

Treatment options for leiomyoma vary. Treatment strategies are typically individualized based on the severity of the symptoms, the size and location of the leiomyoma lesions, the patient's age and their chronological proximity to menopause, and the patient's desire for future fertility. The usual goal of therapy is the relief of the symptoms (which include abnormal uterine bleeding, pain, and pressure). The treatment options range from the use of acupuncture (ancient Chinese method) to the total removal of the uterus and its myoma contents.[20] The gold standard of leiomyoma treatment is surgical intervention. Hysterectomy is the definitive surgical operation, but myomectomy is still commonly performed especially in women who desire future fertility. More recently developed techniques, which include uterine artery embolization (UAE), magnetic resonance-guided focused-ultrasound surgery (MRgFUS), and myolysis, are emerging as minimally invasive alternative procedures. To date, there is no definitive therapeutic agents for the treatment of uterine leiomyomas, which is a reflection of the dearth of randomized clinical trial data demonstrating the effectiveness and safety of medical therapies in the management of symptomatic leiomyomas.[21] Although this article will focus on medical treatment options for uterine leiomyoma, available surgical options will be briefly reviewed.

Surgery

Hysterectomy. Although hysterectomy is considered to be an invasive intervention, the procedure is immediately curative of the symptoms and prevents their recurrence; because of these benefits, it is an attractive option, especially for women who have completed having children. However, it is not devoid of the risks, morbidities, and mortalities of any surgical procedures.[22]

Myomectomy. Myomectomy is the commonly used option for women who have not already completed having children or those who wish to retain their uterus and their fertility. Myomectomy can be approached through the classic laparotomy

incision but can also be performed laparoscopically or more recently, using the robotic approach.[17] The major disadvantage of myomectomy is that 50% to 60% of patients will present with new myomas detected by ultrasound within 5 years following the procedure.[23,24] Additionally, more than one third of these women will require additional surgical intervention for the leiomyomas within 5 years.[25]

Endometrial ablation. Most clinical studies that have evaluated endometrial ablation excluded women with significant myomas. In a recent study that examined endometrial ablation combined with hysteroscopic myomectomy, an 8% risk for a second surgical intervention for uterine leiomyomata after a relatively long period of follow-up (6 years) was reported.[26] It should be taken into consideration that the patient must be properly assessed before being directed toward ablation and ablation should be considered only if a patient of childbearing age has already renounced pregnancy.[27]

Myolysis. Myolysis is the laparoscopic thermal coagulation or cryoablation of leiomyomatous tissues.[28,29] Because of several reported cases of uterine rupture after myolysis, its use in standard practice is currently limited.[30]

Minimally Invasive Procedures Uterine Artery Embolization and Uterine Fibroid Embolization

Minimally invasive options include the delivery of particulate emboli through the uterine arteries to block the blood supply to the uterine leiomyoma vessels.[31,32] It was shown that women who underwent UAE had a shortened hospital stay and a quicker return to work than those who underwent hysterectomy or myomectomy.[33,34] Although pregnancy is possible after UAE, increased incidence of several obstetrics complications, such as miscarriage, preterm labor, placenta previa, and postpartum hemorrhage, have been reported. Synechia is also a potential complication and should be considered in the decisions about embolization procedures.[35] The American College of Obstetricians and Gynecologists (ACOG) concluded that "based on good and consistent evidence (level A), UAE is a safe and effective option for appropriately selected women who wish to retain their uteri, but still limits this recommendation to women who desire no future pregnancy.[36] It is worth mentioning that the risk of radiation exposure and retrograde embolization that could lead to premature ovarian failure is limited but not negligible.[37] The limitation of the use of this technique with big leiomoymata should also be taken into consideration.[38]

Magnetic Resonance-Guided Focused Ultrasound

Magnetic resonance-guided focused-ultrasound surgery is a more recently developed option for the treatment of uterine leiomyomas in premenopausal women who have completed childbearing. It is a noninvasive technique that employs the convergence of multiple waves of ultrasound energy on leiomyoma tissue, which leads to the thermal destruction of the tissue.[39-42] Comprehensive studies to determine the long-term outcome and to identify the optimal candidates for this procedure are still lacking. Comparative studies between this newly developed modality and well-established approaches are also required with regard to the cost-effectiveness of the technique.

Medical Agents for the Treatment of Uterine Leiomyomas

Currently, there are no definitive Food and Drug Administration (FDA)-approved agents for long-term medical treatment of uterine leiomyomata. However, there are several candidate agents that can be used in addition to other approaches in the management of this common benign tumor. Of these agents, gonadotropin-releasing hormone analogues (GnRHa) are FDA-approved agents for the temporary preoperative use to reduce leiomyoma-related blood loss and to correct the ensuing iron-deficiency anemia.[43] Other agents, such as selective estrogen receptor modulators (SERMs), antiprogestins, aromatase inhibitors (AIs), carbegoline, danazol and gestrinone, have been evaluated for the treatment of uterine leiomyomas with varying degrees of success.[44] The unmet challenge for scientists is to develop an inexpensive agent with the ability to shrink leiomyoma size with minimal to no side effects and without interfering with the ovulatory cycles or fertility potential.

Gonadotropin-Releasing Hormone Analogues

After the first purification of GnRH in 1964,[2,45] it has been used extensively in clinical medicine. This was followed by many publications that described the physiology, pharmacokinetics, and pharmacodynamics of GnRH. To date, there are more than 2000 GnRHa with agonistic and antagonistic actions, and many are used for the treatment of various gynecological conditions, such as endometriosis, hirsutism, dysfunctional uterine bleeding, and premenstrual syndrome, as well as for assisted reproduction. The use of GnRHa in the treatment of uterine leiomyomas was first evaluated in the 1980s.[2]

Production of GnRH

The rhythmic release of the master reproductive hormone, the hypothalamic deca-peptide GnRH (gonadorelin), from some 1000 neurons within the hypothalamus depends on a 300-bp promoter region that is referred to as the neuron-specific enhancer (NSE). Gonadotropin-releasing hormone is released in a pulsatile manner and leads to the stimulation, synthesis, and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary.[46,47] Gonadotropin-releasing hormone (whose half-life is approximately 2-4 minutes) is quickly degraded by peptidase and then cleared by glomerular filtration.[48]

Table 1. GnRH, GnRH Agonists' Relative Potency, Route of Administration, and the Dose Regimen[2,51]

	Relative Potency	Route of Administration	Dose Regimen
GnRH	1		
Leuprolide (Lupron)	15	Subcutaneous injection	500-1000 mg/d
		Intranasal	400 mg _4 days
		Intramuscular depot	3.75-7.5 mg/month
			11.25 mg/3 months
Buserelin (Suprefact, CinnaFact)	20	Subcutaneous injection	200 mg/day
		Intranasal	300-344 mg × 4 days
Nafarelin (Synarel)		Intranasal	3 mg/month
		Intramuscular depot	depot 2-4 mg/month
Deslorelin (Ovuplant)	114		
Histrelin (Vantas, Supprelin LA)	210	Subcutaneous injection	100 mg/day
Goserelin (Zoladex)		Subcutaneous implant	3.6 mg/month
			10.8 mg/3 months
Tryptorelin (Decapeptyl, Diphereline, Gonapeptyl, Trelstar)		Intramuscular depot	3 mg/month

Synthetic GnRH analogues. Gonadotropin-releasing hormone analogues have been synthesized for possible clinical use with agonist or antagonist properties to increase the potency and duration of native GnRH (Table 1).[49]

After administration of GnRH or GnRHa, an initial stimulation of pituitary gonadotrophins occurs and is followed by an increased secretion of FSH and LH with an expected gonadal response. However, continuous or repeated administration (in a nonpulsatile fashion) or the administration of supraphysiological doses ultimately produces inhibition of the pituitary–gonadal axis.

Pharmacokinetics

When GnRHa are orally administered, they are readily destroyed by the digestive process; however, they may be parenterally administered via nasal spray or vaginal pessaries. Some GnRHa-containing implants that are capable of slow drug release have been developed to avoid frequent injections, and some implants that deliver analogues for 1 year have also been developed.[50]

Effect on Uterine Leiomyoma

Gonadotropin-releasing hormone analogues can effectively reduce uterine leiomyoma volume, reduce heavy menstrual bleeding, and restore hemoglobin levels by inducing an iatrogenic reversible menopause.[52-56] This can be explained on the molecular level; GnRHa increases apoptosis and decreases angiogenesis and the inflammatory reactions in leiomyoma lesions.[55] Another possible mechanism by which GnRH inhibit the growth of human uterine leiomyoma could be its direct effect on the GnRH receptors which have been identified in leiomyoma[57,58] Those effects result in a 35% to 65% reduction in both the leiomyoma size and the uterine size along with the development of amenorrhea.[36] The only FDA-approved GnRHa for the management of uterine leiomyomas is Lupron Depot (3.75 mg/month) which is administered concomitantly with iron therapy; this approach is indicated for the preoperative hematologic improvement of patients with anemia due to uterine leiomyomas and should not be used for more than 3 months.[59] However, some off-label use for up to 6 months have been reported.[43,60] Unfortunately, the effects of GnRH agonists are temporary, and re-growth of the leiomyomas to their pretreatment sizes within a few months after the cessation of the treatment has been consistently reported.[61] In addition, the symptoms of pseudomenopause and the adverse impact on bone density limit the long-term use of GnRHa. The long-term use for more than 6 months with add-back therapy could be considered to minimize the continued bone loss and the menopausal symptoms,[36] because there is some evidence that add-back therapy can reduce the menopausal symptoms and/or the loss of bone density. However, good-quality research to arrive at definitive conclusions for this approach in uterine leiomyomas is still lacking.[62]

Gonadotropin-Releasing Hormone Analogues With Add-Back Therapy

The "add-back regimens" concept has emerged as a way to overcome the unwanted side effects while maintaining the benefits of GnRHa therapy. Multiple agents may be used as add-back therapy, and they include progestins alone, estrogen alone, combined estrogen and progesterone, tibolone, and raloxifene. The hypothetical concern of whether add-back therapy would compromise the efficacy of the GnRHa turned out to be invalid.[2,63,64] Appropriately selected add-back agents will significantly reduce the side effects, improve the compliance, and enable prolonged therapy without compromising the efficacy of the GnRHa therapy.[61]

Examples of Add-Back Regimens

Progesterone

Medroxyprogesterone acetate (MPA) seems to be a useful addition to GnRHa in women with uterine leiomyomas because

it reduces the GnRHa side effects and possibly prolongs the leiomoma's response to the GnRHa[2,65,66] However, the optimum dosing regimens have not yet been standardized.[2,67-69] Another group[67] has reported that the use of medroxyprogesterone may limit the suppressive effect of GnRH agonists on leiomyomas when compared to the use of GnRHa alone.

Estrogens

The unopposed effect of estrogen only agents, which may lead to endometrial hyperplasia, when used as add-back therapy with the GnRHa limits its use in these cases.[2] A few publications have addressed this issue.[67,70,71] One report compared 3 types of estrogen and recommended the use of the natural estrogen "estriol" due to its tissue-selective actions, which prevent body weight gain and limit the growth of uterine tissues.[71]

Combined Estrogen and Progestagen

The use of estrogen/progesterone as add-back therapy has been shown to be at least comparable, if not superior, to the progestin only add-back regimens based on all of the efficacy and safety parameters that were assessed in one prospective randomized trial.[72] Another prospective randomized study suggested the use of GnRHa plus estrogen/progestin add-back for long-term medical treatment.[73]

Tibolone

Multiple randomized controlled trials (RCTs) addressed the use of tibolone—not available in the United States, yet widely used in Europe as add-back therapy with GnRHa. Tibolone is a synthetic selective tissue estrogenic activity regulator (STEAR). After ingestion, it is converted into 3 metabolites; 2 of these metabolites, the 3α- and 3β-hydroxy metabolites, exert an estrogenic effect through the activation of the estrogen receptor. Tibolone has been used for a long time in the treatment of climacteric complaints and in the prevention of bone loss in postmenopausal women.[74,75] Other studies have evaluated the long-term use (up to 24 months) of combined GnRHa and tibolone for the treatment of uterine leiomyomas and concluded that despite this very long duration of GnRHa use, tibolone reduced the hot flashes, prevented bone loss, and reversed the cognitive effects caused by GnRHa without changing the patient's lipid profile.[43,76]

Raloxifene

The use of raloxifene with GnRHa for 6 months caused a more significant reduction in both uterine and leiomyoma size from baseline compared to the usage of GnRHa and placebo.[77,78] This suggests a synergistic mechanism for GnRHa and raloxifene; in addition, this combination decreased bone mineral density loss and prevented or reduced some of the acute metabolic changes that typically occur with the use of GnRHa alone.[79-82] However, no significant differences were noted in leiomyoma-related symptoms, cognition, mood, overall quality of life or menopausal symptoms.[80]

Preoperative Therapy With GnRHa

The use of GnRHa helps to correct preoperative iron-deficiency anemia, reduce intraoperative blood loss, decrease hospital stay, and to reduce uterine volume and leiomyoma size.[83] Patients who were initially scheduled for a midline open surgical procedure were more likely to be converted to a transvaginal procedure following the use of these agents.[62,77,84] Some of the limitations of this approach include cost, lack of a reduction in menopausal symptoms, and bone demineralization after long-term use.[2,85] A cost-effective study concluded that despite the benefits of the use of preoperative GnRHa, the benefits do not justify the cost.[86] Some reports claim that the preoperative use of GnRHa in myomectomy cases is considered to be a risk factor for the recurrence of leiomyomas because smaller leiomyomas shrink beyond the limits of detection and are therefore overlooked during surgery, but then re-grow when the effects of the GnRHa wear off. However, to date, this claim has not been substantiated in high-quality clinical studies.[77,87] Gonadotropin-releasing hormone analogue renders surgical planes less distinct, perhaps due to softening of the leiomyomas, which makes enucleation relatively more difficult[78,88]; this may explain the increased rate of conversion from laparoscopic myomectomy to open myomectomy in cases of preoperative GnRHa use.[89]

Gonadotropin-Releasing Hormone Antagonists

The third-generation GnRH antagonists display a more tolerable side effect profile compared to the first-generation GnRH antagonists (histamine release and severe allergic reactions) and the second-generation GnRH antagonists (allergy and gel formation); some of the GnRH antagonists approved for clinical use by the US FDA include abarelix (Plenaxis, Serono), cetrorelix (Cetrotide; Serono) and ganirelix (Antagon; Organon International). These agents are usually used as injectables. Gonadotropin-releasing hormone antagonists exert their action through the direct competitive inhibition of GnRH by occupying the pituitary GnRH receptors and therefore blocking the access of the endogenous GnRH and exogenously administered agonists to their receptor sites.[90,91] These agents may induce a deep suppression of gonadotropins and the sex steroids, while avoiding any "flare up" phenomena, which may lead to a reduction in uterine leiomyomas size of up to 50%.[86] One of the major limitations to the wide use of the GnRH antagonists in leiomyoma treatment is the short half-life of these agents and the nonavailability of the depot formulation, thus requiring repetitive dosing (daily for most of the antagonists; Table 2).[92]

Promising GnRH Antagonist (Elagolix)

Elagolix is a new well-tolerated nonpeptide which is used orally and rapidly rendered bioavailable after administration.

Table 2. Third-Generation GnRH Antagonists

		Dose/Route of Administration	Comment
Cetrorelix (Cetrotide)	Antagonist	0.25 mg subcutaneous/d 3 mg subcutaneous/4 days	
Ganirelix (Antagon)	Antagonist	0.25 mg subcutaneous/d	
Iturelix	Antagonist	0.5 mg subcutaneous / day	
Nal-glu	Antagonist	10 mg Subcutaneous / day	
Abarelix (Plenaxis)	Approved 2003-withdrawn 05	100 mg intramuscularly 50 μg/kg per d	Cause for withdraw is economic resons
Azaline B	Laboratory only	5 μg/kg for laboratory animals only	
Degarelix	Modified Azaline B Approved 2008 for prostate cancer	240/80 mg subcutaneously/monthly	Less histamine release—no gel formation—water soluble.

It causes a rapid decline in serum gonadotropins, but the effect of the compound is rapidly reversed after discontinuation. These properties suggest that elagolix may enable dose-related pituitary and gonadal suppression in premenopausal women as part of treatment strategies for reproductive hormone-dependent disease states.[93]

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators are nonsteroidal estrogen receptor ligands that display tissue-specific agonist–antagonist estrogenic actions. They are used frequently in the treatment and prevention of estrogen receptor-positive carcinoma of the breast, in addition to their use as ovulation induction agents.[62,94] Tamoxifen is one of the oldest known SERMs, but it may potentially cause endometrial carcinoma due to its partial agonistic effect on the endometrium.[95] There are no RCTs that have investigated the potential role of tamoxifen in the treatment of uterine leiomyomas; however, a few case reports have suggested that it actually increases leiomyoma growth.[62,96] Raloxifene is another SERM that can be considered theoretically, a candidate therapeutic option for uterine leiomyomas. Raloxifene only slightly affected collagen biosynthesis in control myometrium cells. However, it significantly inhibited collagen biosynthesis in leiomyoma cells[97] and exerted its action at the transcriptional level.[98] A newly developed SERM, "Lasofoxifene," is currently awaiting FDA approval. However, the results of early trials suggest that there were no significant benefits compared to raloxifene for the skeleton, breast, heart, or reproductive tract.[59,99]

Mechanism of Action

The most probable hypothesis that explain SERMs' mechanism of action is that they induce changes in estrogen receptors, which result in differential expression of specific estrogen-regulated genes in different tissues.[100] Every member of the SERM family has its own individual characteristics, which depend on its structure, the type of estrogen receptor they bind to, and the set of molecules that interact with its estrogen receptor/SERM complex in the affected cells, and these characteristics result in either agonistic or antagonistic activity.[101]

Selective Estrogen Receptor Modulators and Treatment of Uterine leiomyoma

All SERMs, with their estrogen blocking activity, would be theoretically expected to exert at least some therapeutic effect on uterine leiomyomas. Raloxifene has been showed to enhance the shrinkage of uterine leiomyomas in postmenopausal women.[102,103] However, a recent report from Italy that addressed the effect of raloxifene on uterine leiomyomas showed that the leiomyoma size in premenopausal women who were administered daily doses of 60-mg raloxifene over a 2-year period exhibited no change in leiomyoma size.[104]

Adverse Events

Tamoxifen is not recommended for women with a prior history of deep venous thrombosis, pulmonary embolus, stroke, or transient ischemic attack because it increases the risk of ischemic stroke, particularly in women who are 50 years of age or older. Additionally, the risk of uterine/endometrial cancer was approximately doubled with tamoxifen use,[105] and the risk of superficial thrombophlebitis was 3 times higher.[92,95] Some of these side effects could be due to the inhibition of cellular glutamine uptake, oxidative stress, and the induction of apoptosis.[106] Selective estrogen receptor modulators are seldom used for the treatment of uterine leiomyomas.[97]

Aromatase Inhibitors

Aromatase inhibitors significantly block both ovarian and peripheral estrogen production within 1 day of treatment.[36] Letrozole suppressed the production of estrogens, particularly estrone and estradiol, by 76% to 79% compared to their baseline levels.[107] The underlying mechanism is the inhibition of the aromatase enzyme which catalyzes the conversion of androgenic substances into estrogens.[108] Recent reports have suggested that aromatase is expressed to a greater extent in uterine leiomyoma tissues of AA women compared to caucasian women, which may contribute to the higher incidence of uterine leiomyomas in AA women.[109] Aromatase inhibitors have been shown to be effective against leiomyomas in limited short-term studies with dosing regimens that included 2.5 mg/d of letrozole and 1 mg/d of anastrozole.[110] One of the major

concerns with the use of AIs is the reported bone loss with prolonged use, which necessitates the concomitant use of oral contraceptive pills or progesterone.[111] A recently published RCT compared the effects of 3 months of AI (letrozole) to that of 3 months of GnRH agonist (triptorelin) on uterine leiomyoma volume and hormonal status.[112] The results showed an advantage of the rapid onset of action of AIs in addition to the avoidance of the flare-up that initially occur with GnRHa. Both treatment options induced significant shrinkage of the uterine leiomyomas and improvement in leiomyoma-associated symptoms.[112] The mean reduction in leiomyoma volume with 3 months' use of anastrazole is 55.7%.[113] The authors suggested that AIs should be considered in women with leiomyomas on a short-term basis or in women who want to avoid surgical intervention to preserve their potential fertility.[114] Another concern with the use of AIs as a treatment option for uterine leiomyoma is its off-label use, which mandates a thorough review with patients prior to the initiation of the therapy.[111] Several RCTs are underway that would hopefully add to our understanding of the potential promising role of AIs in the treatment of uterine leiomyomas.[105]

Antiprogesterones

Estrogen has traditionally been considered to be the most important stimulus for leiomyoma growth, and numerous studies that included cell culture and animal models supported this concept.[115] Surprisingly, recent findings suggest that volume maintenance and growth of human uterine leiomyomas are also heavily progesterone dependent, and hence antiprogesterone could reverse leiomyoma growth effects.[116,117] One potential link between the effects of the 2 key steroid hormones on Uterine leiomyomas (ULMs) is that estradiol induced the expression of the progesterone receptor and supported progesterone action on leiomyoma tissue.[115] Clinical findings also support these laboratory observations; studies have involved the evaluation of mifepristone (RU 486),[118-120] azoprisnil,[110,117] and more recently, CDB-2914 and CDB-4124 (CDB: Contraceptive Development Branch).[121]

Mifepristone

Mifepristone (RU486), a well-known oral antiprogesterone compound, has been used for more than 20 years for multiple clinical indications.[112,122-124] It has recently been evaluated as a potential therapeutic agent for uterine leiomyomas with a dose that ranges from 5 mg to 50 mg over a 3-month period.[125-127] Mifepristone reduced leiomyoma size (26%-74%) and improved leiomyoma-related symptoms (63%-100% induction of amenorrhea). Reported side effects included transient elevations in transaminases, which occurred in 4% of cases as well as endometrial hyperplasia and was detected in 28% of the women who were screened with endometrial biopsies.[126] However, these studies were mostly preliminary with limited numbers of participants and therefore, larger randomized well-controlled trials that include thorough monitoring of liver function and endometrial histology are required to conclusively determine the safety and efficacy of this treatment modality.

Asoprisnil

Asoprisnil (J867, BAY86-5294) is an investigational selective progesterone receptor modulator (SPRM) that was developed for the treatment of progesterone-sensitive myomata. It induces unique morphological changes and is associated with inhibited proliferation of the endometrium and leiomyomas. These changes may lead to amenorrhea, which is usually encountered with its use.[110,129,130] Asoprisnil is a tissue-selective molecule that binds to the progesterone receptors with a 3-fold greater affinity than endogenous progesterone.[125] It reduces the uterine and leiomyoma volumes in a dose-dependent manner while achieving remarkable decreases in menorrhagia scores in women with menorrhagia.[131] Amenorrhea rates also increased as the dose of asoprisnil was increased.[126,129] When asoprisnil was administered daily for longer than 3 to 4 months, significant endometrial thickening and unusual histological appearance of the endometrial glands occurred.[127]

Telapristone Acetate/CDB-4124 (Proposed Trade Names Proellex, Progenta)

CDB-4124 is another SPRM, but it is a relatively pure progesterone antagonist. It was studied in recent years for the treatment of uterine leiomyomas and is still being evaluated to address its safety and dose parameters in premenopausal women.[132] Limited information or publications are currently available on the various clinical trials that have investigated CDB-4124; these studies have either been completed or were terminated due to adverse liver-related events according to the www.clinicaltrials.gov Web site. New clinical trials using lower doses of CDB-4124 have recently been approved by the FDA.

Ulipristal/CDB-2914 (VA 2914, ellaOne, ella)

Ulipristal is an FDA-approved SPRM that is indicated for emergency contraception. It is structurally similar to mifepristone and seems to be effective in the treatment of uterine leiomyomas. It is associated with a reduction in pain, bleeding, and leiomyoma size between 17% and 24%,[133] as well as an improvement in quality of life.[134] However, data on long-term treatment are lacking; and similar to other SPRMs, ulipristal may be associated with endometrial thickening and endometrial hyperplasia.[127,135,136] Large randomized well-controlled clinical trials are needed to evaluate the utility of ulipristal for potential clinical treatment of uterine leiomyomas.[135]

Somatostatin Analogues

Increasing evidence has demonstrated a role for growth factors, such as insulin growth factor I (IGF-I) and IGF-II, in the initiation and progression of uterine leiomyomas.[137-140] Leiomyoma

tissue expresses higher levels of IGF-I/IGF-II receptors compared to normal adjacent myometrium.[131,139] Additionally, these tissues secrete their own IGF-1, probably for autocrine and paracrine use.[140] From a clinical perspective, it has been recently reported that patients with high levels of growth hormone (acromegalic patients) have a higher prevalence of uterine leiomyomas than the general population.[141] Lanreotide, which is a long-acting somatostatin analogue that has been shown to reduce growth hormone secretion, has also recently been evaluated in 7 women with uterine leiomyomas, in Italy.[142] Interestingly, lanreotide induced a 42% mean myoma volume reduction within a 3-month period. These results show that somatostatin analogues may potentially be a new therapy for uterine leiomyomas.[143] The treatment with somatostatin analogues for diseases other than leiomyoma appears to be safe and is usually well tolerated with some reports of gallstone formation.[144,145] However, the lack of clinical trials evaluating the long-term use of somatostatin analogues for severe and adverse health implications—such as decreased life expectancy due to accelerated heart disease observed in adults with growth hormone deficiency—may hinder its future use for leiomyoma treatment.

Cabergoline

Carbergoline is a well-known dopamine agonist that is effectively used in the treatment of prolactinoma and for the inhibition of lactation. A recent study[146] evaluated carbergoline as a therapeutic option for uterine leiomyomas. The rational for such an approach lies in its effect as an inhibitory agent on GnRH release. A group in Iran published a preliminary study in 2007,[146] that favored the use of carbergoline as a medical treatment for uterine leiomyomas, in which they reported a volume reduction of about 50% with 6 weeks of use.[134] The same group performed a subsequent study that compared carbergoline with diphereline, which is a gonadotropin-releasing hormone agonist.[147] They reported comparative results in terms of the shrinkage of the leiomyomas and the improvement in the sonographic, clinical, and intraoperative outcomes.[147] These findings warrant larger controlled trials in the future to clearly assess the potential use of carbergoline in the treatment of uterine leiomyomas.

Danazol

Danazol is a synthetic steroid that inhibits steroidogenesis through multienzymatic actions, in addition to its suppressor effect on sex hormone binding globulin.[148] It reportedly induced a significant 24% volume reduction.[149,150] However, a recent Cochrane study failed to identify any RCTs that compared danazol to placebo or any other medical therapy in women with uterine leiomyomas.[151]

Gestrinone

Gestrinone is a steroid that possesses antiestrogen receptor and antiprogesterone receptor properties in various tissues, including the endometrium.[152] A recent report from Italy evaluated the use of gestrinone in the treatment of premenopausal women with uterine leiomyomas at a dose of 2.5 mg twice per week over a 6-month period.[152] The authors reported a 32% $\pm$ 10% reduction in uterine volume.[152] A subsequent study reported up to 60% leiomyoma shrinkage in size.[153] Gestrinone is a contraceptive agent and also exhibits several unfavorable side effects, such as mild androgenicity, weight gain, seborrhea, acne, hirsutism, and occasional hoarseness.

The Levo-Norgestrel Intrauterine Contraceptive Device

The currently available levo-norgestrel intrauterine contraceptive device (LNG-IUS, Mirena) was primarily developed for contraception.[154,155] The device continually delivers 20 mcg LNG per day to the inner wall of the uterus for at least 7 years,[142,146,156] which causes a continuous, strong suppression of the uterine endometrium.[157] Such high local doses of progestin typically leads to a marked reduction in menstrual blood loss of up to 90%[158-160]as well as a decrease in the number of bleeding days per cycle.[157] Some reports described the use of LNG-IUS in women with uterine leiomyoma-associated menorrhagia and reported significant reductions in menorrhagia without reductions in the myoma or uterine size.[161] Interestingly, another study reported that 64% of women who used the LNG-IUS canceled their plans to undergo a hysterectomy within a 6-month period of the study,[162] which may warrant a cost-effectiveness analysis of LNG-IUS versus hysterectomy in leiomyoma patients who present with severe uterine bleeding. The manufacturer (Bayer HealthCare Pharmaceuticals Inc, Wayne, New Jersey) states that the use of the LNG-IUS is contraindicated with congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity.

In the Pipeline

Vitamin D

Data from our laboratory demonstrate that vitamin D (VitD) inhibits growth and induces apoptosis in cultured human leiomyoma (HuLM) cells.[163] We have also recently demonstrated similar effects in the Eker rat model of uterine leiomyomas.[164] In a separate study, we evaluated the correlation between low serum levels of VitD and the increased risk of having symptomatic uterine leiomyomas.[165,166] We measured both the biologically active 1, 25 dihydroxyvitamin D3 and the precursor 25-hydroxyvitamin D3 in the serum from AA and caucasian women with leiomyomas as well as normal healthy controls. Interestingly, we observed that 1, 25 dihydroxyvitamin D3 is significantly lower in women with leiomyomas compared to normal healthy controls; additionally, we detected lower levels of total serum 25-hydroxyvitamin D3 in women with leiomyomas compared to healthy controls. These findings were observed both in AA women and in caucasian women.

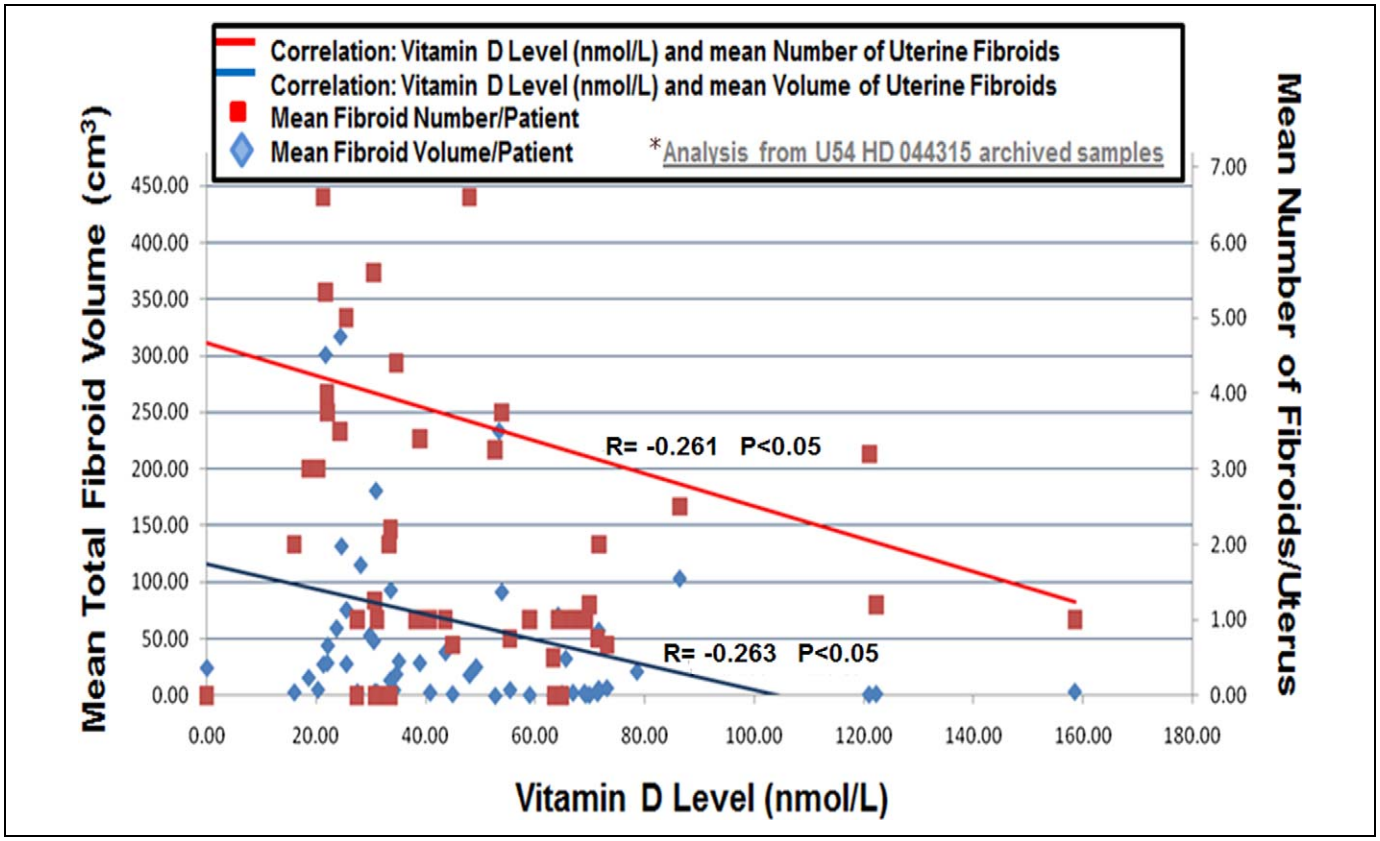

Figure 1. Serum vitamin D3 level (nmol/L) inversely correlates with both mean volume and number of uterine leiomyomas.

Furthermore, we wanted to determine whether serum levels of VitD correlated with disease severity in women with symptomatic uterine leiomyomas. We studied patients (n = 67) with detailed repeated pelvic ultrasound evaluations over a 2-year period with specific measurements of the total uterine volume and the volume of the individual leiomyoma lesions. The patients also had detailed laboratory analysis including serum 25 hydroxyvitamin D3 levels. As shown in Figure 1, we detected a statistically significant negative correlation between the serum VitD levels and the total uterine leiomyoma volume ($P < .05$) and the number of leiomyoma lesions/uterus ($P < .05$).[167] Taken together, our preliminary results suggest a strong dose–response correlation between lower serum VitD levels and increased severity of uterine leiomyomas. This presents an opportunity for the potential use of VitD or its potent analogues as novel treatment options or for the prevention of uterine leiomyomas.

Epigallocatechin Gallate, Green Tea Extract

Epigallocatechin gallate (EGCG), which is the principal catechin, comprises >40% of the total polyphenolic mixture of green tea catechins.[168] Catechines are a group of bioflavonoids that exhibit antioxidant and anti-inflammatory capacity. Chemically, catechines are polyhydroxylated with water-soluble characteristics.[169] Epigallocatechin gallate exhibits various biological activities including potent antioxidant and anti-inflammation capacity.[170] Previous studies have shown that EGCG inhibited the growth of various human cancer cells, such as epidermoid carcinoma cells,[171] hepatoma cells,[172] prostate carcinoma cells,[173] and breast cancer cells.[174] In our laboratory, we studied the effect and potential mechanisms of EGCG action on HuLM cells.[175] We clearly showed that EGCG inhibits the proliferation of HuLM cells and induces apoptosis. These results suggest that EGCG may be a potential antiuterine leiomyoma agent that acts through multiple signal transduction pathways. Additional validation of these findings was achieved using orally administered EGCG to shrink preexisting subcutaneous leiomyoma lesions in immunecompromised mice.[176] Those findings motivated us to initiate a currently ongoing double-blind placebo-controlled clinical trial to evaluate the possible clinical role of EGCG in women with symptomatic uterine leiomyomas.

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Declaration of Conflicting Interests

Dr Al-Hendy was a site principal investigator in phase III clinical trials of "Azoprisnil" and "Pro-ellex." Dr Mohamed Sabry has nothing to disclose.

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