Medical Management of Uterine Fibroids

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Abstract Uterine leiomyomas are the most common benign tumors of the uterus. Though benign, they can affect the quality of life for many women. Compared with the standard surgical treatments, medical therapy is attractive and avoids possible surgery-related complications. No medical therapy currently exists that can induce rapid regression of the myoma and symptoms with minimal side effects without affecting fertility. This review evaluates medical treatments that are currently available for the treatment of uterine fibroids.

Keywords Medical therapy · Uterine myoma · Uterine fibroid · Gonadotropin-releasing hormone agonists · GnRH · GnRH antagonists · Raloxifene · Aromatase inhibitors · Anastrozole · SERMs · Mifepristone · Progesterone receptor modulators · Dienogest · Asoprisnil · Cabergoline · Pirfenidone

Introduction

Uterine fibroids are slowly growing, solid pelvic tumors [1•]. The prevalence ranges between 5.4% and 77% of women, depending on the method of diagnosis [2]. Uterine fibroids mainly originate from individual smooth muscle cells of the uterus [3]. The smooth muscle cells of the uterine blood vessels may also be a source [4]. Although benign, fibroids may have a major impact on the quality of life of almost 50% of the women who are symptomatic. Symptoms include menstrual disturbances (commonly menorrhagia), which affects 30% of women, pressure symptoms, pregnancy-related problems, and infertility [3, 5]. Uterine fibroids (especially submucosal myomas) also are associated with adverse reproductive outcomes [6].

Treatment of myoma depends on symptoms, patient age, fertility, previous obstetric performance, and the location and size of the myoma [1•]. Because the tumors are hormonally dependent, develop during the reproductive period, and are suppressed by menopause, current medical treatments involve mainly hormonal manipulations [7]. Studies have shown the presence of estrogen and progesterone receptors with higher concentrations in myomas than in the surrounding endometrium [8, 9]. Progesterone seems to have a dual effect on myomas by altering local growth factors. It is suggested that one effect of progesterone is to stimulate myoma cell growth and survival by increasing epidermal growth factor (EGF) and Bcl-2 protein expression, as well as by decreasing tumor necrosis factor (TNF)- α expression in those cells; the second effect is to inhibit myoma cell growth by decreasing insulin-like growth factor-I (IGF-I) expression in uterine fibroid cell cultures. EGF and IGF-I are growth factors and TNF- α and Bcl-2 protein are apoptosis-related factors in cultured uterine fibroid cells [10]. There are also nonhormonal agents that are suggested to treat uterine fibroids on the base of their ability

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to inhibit fibroid cellular growth and collagen synthesis or to increase cellular apoptosis.

The growth pattern of uterine fibroids is not predictable. In a study using MRI to evaluate the growth of fibroids, the authors reported periods of growth spurt of over 30% in 3 months in 37 of 101 women [11•]. Because the growth patterns of fibroids vary in different periods, the prediction of growth patterns and decisions about any intervention can be difficult.

This article reviews the available therapies for medical management of uterine fibroids and the risks and benefits of each medication.

Why Medical Treatment?

Compared with standard surgical treatments, medical therapy, which avoids possible surgery-related complications, is attractive. Currently, medical treatments are used for short periods in symptomatic women. Medical treatment can have several objectives:

- Improving the hematologic status of women who are anemic before surgery
- Reducing the size of fibroids, to allow surgery using a minimally invasive technique. For those who require a laparotomy, a Pfannenstiel incision could be used instead of a vertical incision for patients with smaller fibroids.
- Avoiding surgery in symptomatic women near menopause
- Extending preoperative time to stabilize a serious medical condition
- Providing a nonsurgical treatment to women who desire to preserve their uterus.

Oral Contraceptives

Combined oral contraceptive pills and progestin-only pills are effective for the treatment of abnormal uterine bleeding. These therapies can induce endometrial atrophy and stabilize the endometrium [12]. However, the myoma size does not change [7, 13]. Further, evidence shows that estrogens and progestins can act as growth stimulators for uterine myomas [14].

Levonorgestrel-Releasing Intrauterine Devices

The levonorgestrel-releasing intrauterine device (LN-IUD) releases 20 µg/day of 19-norprogesterin into the uterine cavity. It has been proven to reduce the amount and duration of menstrual blood loss [15, 16] by inhibiting endometrial proliferation [17]. However, large uterine size increases the risk of expulsion and decreases its efficacy [18].

Steroid Synthesis Inhibitors

Gonadotropin-Releasing Hormone Agonist

Gonadotropin-releasing hormone agonist (GnRHa) is the most effective drug for uterine myomas. It induces an initial stimulation of gonadotropin, followed by inhibition of the pituitary-gonadal axis, and induces a hypoestrogenic state. In a clinical trial, administration of GnRHa resulted in amenorrhea, almost 35% shrinkage of myoma, and 61% reduction of uterine volume [19]. The use of GnRHa is associated with increased hemoglobin concentrations [20]. Most myomas return to their initial size within about 6 months after discontinuation of treatment. GnRHa induces a generalized hypoestrogenic state that includes hot flushes, vaginal dryness, headache, depression, hair loss, musculoskeletal stiffness, and bone loss [1•, 21]. Various types of add-back therapy can be used to counteract the unwanted hypoestrogenic effects of GnRHa therapy:

GnRHa with Tibolone

Tibolone is pharmacologically categorized as a combination of estrogen and progestin. Several randomized clinical trials have shown that administration of GnRHa plus tibolone (2.5 mg/day) for 6 months in women with fibroids reduced vasomotor symptoms and prevented bone loss without compromising the therapeutic effect of GnRHa [22, 23].

GnRHa with Raloxifene

Raloxifene, a selective estrogen receptor modulator (SERM), does not reduce menopausal symptoms of estrogen deficiency when used as add-back therapy, but it does reduce bone loss and seems to act synergistically to reduce the fibroid volume in postmenopausal women [24, 25].

GnRHa with Progesterone

Medroxyprogesterone acetate (MPA) can be used as an add-back therapy with GnRHa. A randomized study showed that it reduced GnRHa vasomotor symptoms [26].

GnRHa with Combined Estrogen and Progesterone

A combination of estrogen and progesterone has been used effectively to reduce hypoestrogenic symptoms and is even superior to GnRHa plus progesterone in the treatment of uterine fibroids, with regard to efficacy and some safety parameters. In one study, GnRHa alone was used for 51 women with uterine fibroids for 12 weeks, and then add-back therapy was begun, using two methods. The first group received a combination of estrogen and progesterone, and the second group received progesterone as add-back therapy. In

the first group, combination therapy induced no significant regrowth in the mean uterine volume, but the second group had regrowth of uterine volume to 92% of pretreatment size in 52 weeks of therapy. Also, HDL cholesterol decreased significantly in the progestin add-back group, an effect that was not seen in the combination group [27].

GnRH Antagonists

GnRH antagonists act by competitive inhibition of the pituitary GnRH receptors, leading to immediate suppression of the pituitary gland. They are associated with a shorter duration of treatment and flexibility in the degree of pituitary suppression in a dose-related manner [1•, 5, 21]. Three GnRH antagonists have been approved by the US Food and Drug Administration (FDA): cetrorelix (Cetrotide; Serono International SA, Geneva, Switzerland), ganirelix (Orgalutran/Antagon; Organon, Oss, The Netherlands), and abarelix (Plenaxis; Praecis Pharmaceuticals Inc., Waltham, MA, USA) [5, 21].

In one study, ganirelix induced 42.7% shrinkage in uterine fibroids with a median treatment duration of 19 days [28]. It increased apoptosis of myoma cells *in vivo* [29]. Its acceptability has been limited by its hypoestrogenic side effects, its temporary effectiveness, and the requirement for daily injections.

Aromatase Inhibitors

Aromatase is needed to convert androstenedione to estrone and testosterone to estradiol [21]. Aromatase mRNA is expressed in myoma but is not expressed in normal myometrial cells [30, 31]. Further, estrogen concentration in myoma tissue is greater than in the surrounding myometrium. Some studies have shown that leiomyoma tissues are a source of estrogen. Leiomyoma cells express an estrogen synthetase as well as aromatase and convert circulating androgens to estrogen [30, 32, 33]. Estrogen secreted by leiomyoma tissue may reach a sufficient concentration within the local compartment to support its own growth, allowing independence from ovarian estrogen [34, 35].

Aromatase inhibitors (AIs) were first used to treat McCune-Albright Syndrome (MAS). MAS, a rare disorder, is defined as the triad of peripheral precocious puberty (caused by GnRH-independent estrogen synthesis), café-au-lait skin pigmentation, and fibrous dysplasia of bone. AI was used to inhibit estrogen synthesis in these patients. A nonselective AI, aminoglutethimide, has also been used for advanced breast cancer, to block the synthesis of estrogen. Other generations of AIs that were developed to selectively inhibit the action site include anastrozole (Arimidex®: Astra-Zeneca, Macclesfield, UK) and letrozole (Femara®, Novartis). Both of these are nonsteroidal AIs.

Both fadrozole [36, 37] and anastrozole [38, 39•] have been shown to reduce myoma volume effectively. These substances are associated with rapid onset of action, and the initial flare-up effect of GnRH agonists is absent. Shozu reported 71% reduction in myoma volume after 8 weeks of treatment with fadrozole [36], and no significant change in estradiol level was reported [37, 39•].

We recently studied the effect of letrozole, randomizing women with myoma into groups treated with letrozole or GnRHa. Similar to previous studies with fadrozole and anastrozole, we found that letrozole decreased uterine myoma volume. Rapid onset of action and avoidance of initial flare-up may be advantageous for short-term management of women with myomas, especially those with unexplained infertility. This AI can also be used preoperatively [40••].

In a study among women with breast cancer, anastrozole was associated with decreased bone mineral density after 5 years of treatment [41]. Letrozole may be preferred because it does not cause hypoestrogenemia and its related adverse effects, perhaps because the small dose of letrozole used in our study (2.5 mg) is insufficient to inhibit the production of estradiol in the ovaries [40••]. The long-term efficacy and possible complications of letrozole treatment for the treatment of uterine myoma remain to be seen.

Catechol-O-Methyltransferase Inhibitor

Catechol-O-methyltransferase (COMT) is an enzyme that converts catechol estrogens to their methylated forms. Increased COMT activity is associated with increased estrogen levels and increased uterine fibroid growth. It has been reported that COMT expression is higher in uterine fibroid than in normal myometrium [42]. COMT inhibitor can potentially suppress estrogen synthesis and decrease uterine fibroid growth. Clinical studies are yet to be conducted.

Steroid Receptor Modulators

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) are nonsteroidal agents that bind to estrogen receptors and induce different expression of specific genes in different tissues. SERMs include clomiphene, tamoxifen, raloxifene, and idoxifene. These drugs have agonistic or antagonistic activity depending on the type of estrogen receptor that they bind to and the set of molecules that they interact with in different tissues [43, 44]. For example, raloxifene has estrogen antagonistic action in the uterus and breast but estrogenic activity in bones and vessels.

Tamoxifen acts as an estrogen agonist on bone and uterus and as an antiestrogen in breast tissue. Tamoxifen inhibits myoma cell growth *in vitro* [45, 46]. Because of its side

effects, such as endometrial hyperplasia and ovarian cysts, it has not been used to treat uterine fibroids. Raloxifene has been found to reduce the volume of the uterus and fibroids in postmenopausal women. Its effect in premenopausal women is dose-dependent; it does not always reduce the size of fibroids [24, 25, 47].

In a study, the authors compared raloxifene (60 mg daily) with leuprolide acetate (3.75 mg monthly for six cycles) versus leuprolide alone [24]. They found that the size of myoma and related symptoms were significantly decreased with the combined treatment. Extension of the treatment for 12 or 18 months was not associated with further reduction [48]. Raloxifene does not change the lipid or glucose profile and does not stimulate the endometrium. It preserves bone density but is associated with hot flushes. A recent Cochrane review that included three randomized controlled trials using SERMs did not find evidence of a beneficial effect of SERMs on the treatment of uterine fibroids [3].

Progesterone Receptor Modulators

Compared with the surrounding endometrium, uterine myoma has a high concentration of progesterone receptors [8, 9]. Mifepristone, onapristone, and ZK 230211 are pure progesterone receptor modulators. Steinauer and colleagues reviewed six clinical trials of mifepristone treatment for myomas [49]. They included 166 premenopausal women who were treated with 5 to 50 mg of mifepristone for 3 to 6 months. They found a 26–74% decrease in mean myoma volume, a 27–49% decrease in uterine volume, and a 75% reduction in myoma symptoms. Side effects include hot flushes, elevation of hepatic enzymes, and endometrial hyperplasia. Bone density was not affected [50, 51]. Bagaria and colleagues used 10 mg per day of mifepristone for 3 months and found that the treatment group had reductions in menstrual blood loss and uterine and myoma volume. However, 63.1% of the patients developed endometrial hyperplasia without atypia [52].

Selective Progesterone Receptor Modulators

Among the selective progesterone receptor modulators (SPRMs) are J compounds (J867 [asoprisnil], J956, and J1042), which have agonist/antagonist activity [21]. Compared with progesterone, asoprisnil has a high tissue selectivity and higher binding affinity to progesterone receptors [53]. It induces amenorrhea and reduces uterine fibroid volume in a dose-dependent manner [54, 55], and it reduces uterine artery blood flow [56]. Asoprisnil has marginal abortifacient activity and no antiglucocorticoid effect [57–60]. This drug does not induce estrogen deprivation symptoms or breakthrough bleeding. It induces endoplasmic reticulum stress [61] and TNF-related apoptosis in cultured human leiomyoma cells [62].

Following studies showing that CDB-2914 decreased the volume of uterine fibroids [63], other investigators found that it inhibits proliferation, stimulates apoptosis, inhibits expression of angiogenic factors, and downregulates vascular endothelial growth factor in cultured myoma cells but not in normal myometrial cells [64, 65]. Dienogest is another potent progestin without androgenic, mineralocorticoid, or glucocorticoid properties. Dienogest 2 mg daily showed equal efficacy to GnRHa in reducing the pain of endometriosis over a 24-month period and induced shrinkage of coexisting uterine fibroids [66]. It appears that endometrial pathology could be induced by progesterone receptor modulators [67].

Androgen Therapy

Androgens have anti-estrogen and anti-progestin activity. Two androgens, danazol and gestrinone, have been studied for the management of uterine fibroids.

Danazol

Danazol is an isoxazole derivative of the synthetic steroid 17 α -ethinyl testosterone. It inhibits gonadotropin secretion and endometrial growth [19]. Traditionally, danazol was widely used for the treatment of endometriosis, usually at dosages of 100 to 400 mg per day. Studies showed that danazol can reduce the size of fibroids by about 23.6% [1]. The side effects consist of acne, oily skin, voice changes, hirsutism, weight gain, and hepatocellular damage [50, 68]. A recent review of the use of danazol for uterine fibroids concluded that the benefits of danazol do not outweigh its risks [69].

Gestrinone

Gestrinone is a tri-ene derivative of ethinyl-nor-testosterone. Gestrinone at a dose of 2.5 to 5 mg two or three times a week for 6 months could induce significant reduction in the size of uterine fibroids [70]. This medication induces undesirable androgenic properties that limit its use [71].

Miscellaneous Agents

Other agents have been advocated for the treatment of uterine fibroids. Their mechanisms include inhibiting cell growth and proliferation by special growth factors in myoma cells or increasing cellular death or apoptosis.

Antifibrotic Agents: Pirfenidone

Myofibroblasts are components of uterine fibroids that produce collagen for the extracellular matrix (ECM). A study

showed that ECM genes in uterine fibroid have dysregulated expression. Transforming growth factor- β (TGF- β) is a profibrotic cytokine that regulates cell growth, proliferation, and fibrosis [72]. Pirfenidone, an antifibrotic drug, inhibits TGF- β , DNA, and collagen synthesis in cultured uterine fibroid cells [73]. Pirfenidone reduces mRNA for collagen type I and III in culture media. In one human study lasting 3 months, pirfenidone reduced the size of myomas [74].

Cabergoline

Cabergoline, a lysergic acid–derived dopamine agonist with a long half-life, is widely used for the treatment of hyperprolactinemia. The hypothesis behind its use is its inhibitory effect on GnRH. Cabergoline is easily tolerated, requires widely spaced doses, has few side effects, and can be considered a good choice. One study comparing cabergoline and GnRHa found that cabergoline was equally effective in reducing the size of uterine fibroids [75].

Growth Factor–Mediated Therapy

It is hypothesized that growth hormone can induce uterine fibroid growth by stimulating the growth factor receptors. Women with acromegaly have a higher prevalence of uterine fibroids. One study used lanreotide depot, a long-acting somatostatin analogue, for 3 months in seven women and found a 41.6% reduction in uterine fibroid volume [76].

Antagonists of Retinoic Acid

In animal studies, a combination of retinoid acid and estrogen led to myoma formation in the uterus of ovariectomized guinea pigs [77]. Some forms of retinoic acid nuclear receptors have greater expression in uterine fibroid cells than in myometrial cells. Accordingly, an antagonist of retinoic acid can be effective in causing regression of myoma cells. Clinical studies are yet to be done.

Kuei-chih-fu-ling-wan: Chinese Herbal Drug

Kuei-chih-fu-ling-wan (Keishi-bukuryo-gan; KBG) is a Chinese herbal drug. In a study of 110 women treated with this herbal drug, hypermenorrhea and dysmenorrhea improved in more than 90% and shrinkage of myoma occurred in more than 60% of cases [78]. More study is needed.

Hypoglycemic agents

Insulin-like growth factor-I (IGF-I) is suggested as an important growth factor for the growth of uterine fibroid [79], and gene studies have confirmed this concept [80]. Pioglitazone, a drug used for diabetes mellitus, inhibits cell proliferation in

uterine fibroid and myometrium [81]. Thiazolidines are a class of oral hypoglycemic agents that increase insulin sensitivity. The mechanism of action is not completely known, but they bind to and activate one or more peroxisome proliferator-activated receptors (PPARs) [82]. In theory, these substances may work in treating uterine fibroids.

Heparin

In vitro study has shown that heparin inhibits the proliferation of smooth muscle cells of leiomyoma [83].

Conclusions

Medical management of uterine fibroids is a temporary treatment. Symptomatic women with uterine fibroids who wish to retain the option of fertility and those who are poor surgical risks are candidates for medical treatment. Today, GnRHa is the most widely accepted treatment. However, aromatase inhibitors and selective progesterone modulators may be preferable because of their lack of severe hypoestrogenic effects. Randomized trials with long-term follow-up are needed to explore the efficacy of a number of substances: aromatase inhibitors, cabergoline, COMT inhibitors, SERMs (asoprisnil, CDB-2914, dienogest), antifibrotic agents such as pirfenidone and somatostatin analogues. Also Invention of new generations of long-acting GnRH antagonists may be helpful for medical management of uterine fibroids.

Improved basic studies on the biology of growth in uterine fibroids also will lead to improved treatment. Topics to be studied include growth factors and gene expression, and how they can control and regulate normal and abnormal cell growth.

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