The Medical Treatment of Uterine Fibroids

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Abstract

Uterine fibroids are the most common benign tumor in women, and cause many symptoms. The treatment for these tumors has traditionally been surgical. However, a variety of medical therapies are now available for use. These drugs are primarily utilized as preoperative adjunctive therapy to ease the difficulty of surgery. However, some may have potential as long-term medical treatments, allowing the patient to delay or even avoid surgery. Current medications include GnRH analogs, selective estrogen receptor modulators, aromatase inhibitors, progesterone receptor modulators, and a variety of other less thoroughly evaluated medications. In addition, a number of drugs are in development that are designed to attack novel, specific targets in the leiomyoma growth, and maintenance process.

1 Introduction

Uterine leiomyomata, also known as fibroids, are the most common benign tumors in women of reproductive age. The prevalence of these benign tumors increases with age, and by the age of menopause, ultrasonographic evidence of fibroids can be found in 80 % of African–American women and 70 % of Caucasian–American women (Baird et al. 2003). These tumors can produce a variety of symptoms, including abnormal uterine bleeding, dysmenorrhea, pressure effects such as constipation, urinary frequency, and pelvic pain, and reproductive issues such as infertility, recurrent pregnancy loss, preterm labor, fetal malpresentation, and obstetrical hemorrhage.

The principle treatment for uterine fibroids, when symptomatic, has traditionally been surgical. Hysterectomy is commonly employed in the woman no longer desiring reproductive potential, while those wishing to conserve fertility generally opt for myomectomy (laparotomic or

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laparoscopic). Recently, minimally invasive interventions such as uterine artery embolization and myolysis via ultrasound, electrosurgical heat, or cryotherapy have been investigated and implemented (Olive 2000).

Medical therapy for uterine fibroids has long been desired and considered. However, lack of understanding of the biology and biochemistry of myomas, as well as discouraging data from a few available treatment trials led to sparse enthusiasm for this approach. Fortunately, our knowledge of the mechanisms of growth of uterine fibroids has increased dramatically in recent years, as has the available armamentarium for medical interventions. Today, there are numerous potential directions for both the clinician and researcher to proceed when trying to attack these tumors medically.

This chapter will review the bioendocrinology of fibroids as well as the available medical treatments and evidence of their effectiveness. Finally, a rapid review of experimental treatments, currently being investigated in animal models or cell culture, will be included.

2 Potential Roles for Medical Treatment

Medical therapy for fibroids is often used for short-term relief of symptoms. Abnormal uterine bleeding can often be treated effectively for a period of time until either menopause occurs or a more permanent treatment is instituted. Mass effects from large fibroids, such as constipation, bladder frequency or urgency, or ureteral obstruction with resulting hydroureter and hydronephrosis, can also be relieved for a time.

The primary use for this approach today is in the preoperative patient. Reduction of symptoms prior to surgery may improve the patient's course; a common example is the cessation or reduction of bleeding in the anemic patient. In addition, preoperative medication may allow for the conversion of a technically difficult procedure into an easier surgery by reducing the size of the tumors.

Long-term therapy, although infrequently used, has significant potential. The role of such treatment has been infrequent to date, due to a lack of data to support its use as well as concerns regarding adverse effects and costs. Exploration of this concept in the future, especially with newer, more targeted therapies, will inevitably occur.

A final role proposed for medical therapy of leiomyomata is for prophylaxis against development of the tumors in those at high risk, or recurrence in women previously treated. To date there has been little work in this arena. As we increase our understanding of the endocrinology, biochemistry, and genetics of fibroids, prophylaxis may begin to have a prominent role in research and clinical practice.

3 Endocrinology of Fibroid Growth and Maintenance

Fibroids are clearly affected by the hormonal environment of the patient, as confirmed by the clinical observation that they generally first develop during reproductive years and regress following menopause. Estrogen clearly plays a role in fibroid growth and development. The growth of these tumors is up-regulated by estrogen (Walker 2002). Leiomyomata contain estrogen receptors, and more are present in the tumor than in surrounding myometrium (Otubu et al. 1982; Rein et al. 1990; Brandon et al. 1995; Bakas et al. 2008). In addition, aromatase is present in significant amounts (Bulun et al. 1994). These factors produce a hyperestrogenic environment within the fibroid.

Progesterone too seems to have a growth-promoting effect upon fibroids. Peak mitotic activity can be found in the luteal phase (Kawaguchi et al. 1989; Tiltman 1985) and high doses of progestational agents will enhance mitotic activity. Progesterone receptor levels are elevated in fibroids, probably because of up-regulation by the high levels of estrogen.

Estrogen and progesterone induce tumor growth by a variety of mechanisms. Progesterone increases BCL2 gene expression, which results in the production of bcl-2 protein, an inhibitor of apoptosis and a stimulator of cell replication (Yin et al. 2007). In addition, the expression of a large number of growth factors is induced by steroid hormones. Epidermal growth factors, insulin-like growth factors, and their receptors are overexpressed in these tumors, a direct result of high levels of estrogen exposure (Fritz and Speroff 2011).

Knowledge of these pathways for fibroid growth has given researchers a bevy of potential targets for medical treatment of the tumors. The results are a wide variety of drugs, each designed to target some aspect of this hormonal cascade within the fibroid.

4 Available Medical Treatments

4.1 GnRH Analogues

4.1.1 GnRH agonists

Ovarian hormone secretion is dependent upon the functionality of the hypothalamic-pituitary-ovarian axis. The hypothalamus secretes gonadotropin-releasing hormone (GnRH) which stimulates pituitary secretion of the gonadotropins follicle-stimulating hormone (FSH) and leutinizing hormone (LH). These hormones, in turn, stimulate the ovary, resulting in follicular growth, ovulation, and the

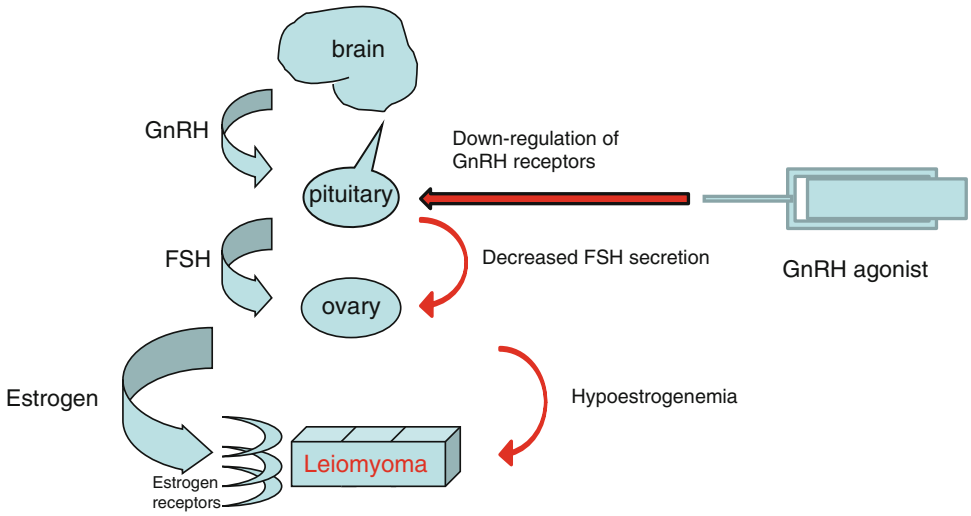

Fig. 1 Mechanism of action of Gonadotropin-releasing hormone agonists (GnRH-agonists) on the hypothalamic-pituitary-ovarian axis in the presence of uterine fibroids

production of steroid hormones. GnRH release is pulsatile, and precise amounts and rates of GnRH secretion are required for optimal stimulation of FSH and LH production and release.

GnRH agonists are peptides that are modifications of the native GnRH molecule. Several agents have been developed that differ from the native hormone with respect to the specific amino acid sequence. All are designed to either increase receptor affinity or decrease GnRH degradation. Their use, therefore, leads to persistent activation of GnRH receptors. This activation results in an initial release of gonadotropin previously produced and stored in the pituitary. However, the release is rapidly followed by down-regulation of the GnRH-receptor expression and profound suppression of gonadotropin secretion. As a result, sex-steroid production in the ovary falls to levels similar to those seen after castration. This hypoestrogenic, hypoprogestogenic state creates an adverse environment for the fibroid (Fig. 1).

Three GnRH agonists are currently approved by the Food and Drug Administration for the treatment of endometriosis in the United States: leuprolide acetate, goserelin acetate, and nafarelin acetate. They differ with respect to dose and mode of administration. Leuprolide comes in a depot form and is administered intramuscularly at a dose of 3.75 mg monthly or 11.25 mg every 3 months. Goserelin can be administered as a monthly 3.6 mg subcutaneous implant or a 3 month 10.8 mg implant. Nafarelin is an intranasal spray, with 200 mcg administered per pump; the daily dose ranges from 400 to 1600 mcg.

Most adverse effects of GnRH-agonist therapy are related to hypoestrogenemia and include vasomotor symptoms, insomnia, and urogenital atrophy (vaginal dryness, urinary urgency and frequency, and painful intercourse). Other common side effects include headache, decreased libido, irregular vaginal bleeding, depression, arthralgia, myalgia, irritability, fatigue, and decreased skin elasticity (Table 1) (Olive 2008).

The most worrisome effect of the drug is loss of bone mineral density, which occurs at a rate of roughly 6 % annually (Hornstein et al. 1998). This side effect is largely responsible for the hesitancy to use GnRH agonist for extended periods of time. Another concerning side effect is memory impairment, which effects up to 44 % of those treated. Fortunately, this adverse phenomenon is completely reversible with discontinuation of the drug (Newton et al. 1996; Sherwin and Tulandi 1996).

An adverse effect unique to the use of these drugs for the treatment of fibroids is significant vaginal hemorrhage roughly 5–10 weeks after initiation of medication. This event is due to degeneration and necrosis of submucous myomas, and occurs is approximately 2 % of treated women (Friedman 1989).

The long-term side effects of GnRH agonists can be minimized or eliminated by adding back a small amount of sex steroids, similar to the replacement hormone dosages for menopausal women. A number of different regimens have been utilized, including estrogen/progestin, progestin alone (medroxyprogesterone or norethindrone), and androgen (tibolone). All reduce vasomotor symptoms, but progestins derived from progesterone (such as medroxyprogesterone) tend to preserve bone less well than norethindrone, whose breakdown products include ethinyl estradiol (Chwalisz et al. 2012). Such therapy can begin with the initiation of the medical therapy, or can be delayed for a period of time to allow for unopposed GnRH action.

GnRH agonists are most commonly used as a preparatory treatment for surgery. When treated for at least 3 months, uterine size is reduced to 30–65 % (Friedman et al. 1988; Carr et al. 1993; Minaguchi et al. 2000). Symptomatic relief is often achieved during this time, as bleeding is generally reduced and pressure effects relieved

Table. 1 Adverse effects of gonadotropin-releasing hormone agonist therapy

Common (>60 % of patients)
Hot flashes
Less common (20–60 % of patients)
Headache, insomnia, memory disorder, and significant temporary bone mineral density loss (if used 6 months or less)
Infrequent (2–19 % of patients)
Significant and persistent bone mineral density loss, anxiety, dizziness, asthenia, depression, vaginal dryness, dyspareunia, weight change, arthralgias, myalgias, alopecia, peripheral edema, breast tenderness, irritability and fatigue, decreased skin elasticity, decreased libido, nausea, altered bowel function, and irregular vaginal bleeding
Rare (<2 % of patients)
Vaginal hemorrhage, allergic reactions

(Benagiano et al. 1996). When patients are anemic from excessive uterine bleeding, the use of GnRH agonist preoperatively has been a strategy used to allow increase in hemoglobin levels. Furthermore, this approach often decreases blood loss at surgery. However, one caveat often mentioned by surgeons (but heretofore undocumented in the literature) is that pretreatment softens the myomas, making complete removal more difficult.

For the hysteroscopic removal of submucous myomas, GnRH pretreatment has several particular advantages. First, when removing fibroids by pieces (as with a resectoscope) rather than as a single, intact entity, a reduction in volume becomes much more meaningful. Second, endometrial atrophy will improve visualization. Finally, decreased vascularity should minimize blood loss and fluid intravasation.

It must be kept in mind that the effect of GnRH agonist reduces leiomyoma cell size and is not cytotoxic. With cessation of the drug there is a return in fibroid size within 3–4 months. This would imply that its use as a stand-alone therapy would be extremely limited. One such situation would be the use of GnRH agonist to treat women close to menopause in an attempt to avoid surgical intervention. However, intermittent, long-term use in women with fibroids may be feasible; in a study of women treated with the medication for abnormal uterine bleeding attributable to fibroids, there was symptomatic improvement in half for up to 6 months following discontinuation (Scialli and Levi 2000). Further investigation is clearly needed to evaluate this interesting concept.

4.1.2 GnRH Antagonists

GnRH antagonists are analogs of the GnRH molecule that act by directly competing for and occupying pituitary GnRH receptors. This blocks access of the GnRH molecule to these receptors, resulting in immediate pituitary suppression of gonadotropin secretion. This avoidance of the initial gonadotropin flare seen with GnRH agonists allows the antagonist to cause a clinical effect much more quickly, generally within 2 weeks. It is also rapidly reversible with discontinuation of the drug.

Similar amounts of shrinkage of fibroids are seen with antagonists as with agonists (Felberbaum et al. 1998, 2001; Gonzalez-Barcena et al. 1997; Flierman et al. 2005). Currently, long-acting antagonists are not available in the US, but should they become available this drug class will likely supplant GnRH agonists as a preoperative therapy, due to the more rapid onset. Exactly this pattern is seen in countries where GnRH antagonists are available and have begun to cause a decline in usage of GnRH agonists.

5 Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) are nonsteroidal estrogen receptor ligands that act as estrogen agonists in some tissues and as receptor antagonists to block estrogen action in others. Different SERMs behave differently in each tissue in which they act; the specific action is determined by their structure, the estrogen receptor to which they bind, and other interacting molecules in the tissue. As an example, tamoxifen and raloxifene, two well-known SERMs, both have estrogen antagonist effects upon mammary tissue. However, raloxifene is also an estrogen antagonist in endometrium, whereas tamoxifen is an agonist in uterine tissue.

The ability to block estrogen action means that this class of drugs has a potentially therapeutic effect in the treatment of fibroids. However, it is critical to find the SERM with the correct combination of actions in other locales. Tamoxifen has not been used in the treatment of myomas because of its tendency to produce endometrial hyperplasia (Neven et al. 1989). In addition, case reports suggest that tamoxifen may be agonistic in myometium and fibroids as well. Conversely, raloxifene's agonist/antagonist profile seems much better suited to this purpose.

As should be expected, the side effect profile of a SERM is primarily dependent upon its actions in various tissues. For raloxifene, the principal side effect is vasomotor symptomatology, as the antagonistic effect predominates in the central nervous system. The most critical side effect, however, is the thrombogenic nature of this medication, an estrogen-like activity in the liver that raises the risk of a thromboembolic event threefold (Ettinger et al. 1999). For this reason, leg pain and respiratory complaints must be taken seriously in women treated with this drug, and it is likely contraindicated in women with known thrombophilias.

Initial studies with raloxifene demonstrated that 60 mg daily was sufficient to significantly decrease the size of the tumors for up to a year in postmenopausal women (Palomba

EFFECTIVENESS OF COMBINED GnRH ANALOGUE PLUS RALOXIFENE ADMINISTRATION IN THE TREATMENT OF UTERINE LEIOMYOMAS: A PROSPECTIVE, RANDOMIZED, SINGLE BLIND, PLACEBO CONTROLLED CLINICAL TRIAL

	GnRH-a + raloxifene	GnRH-a + placebo	P value
Patients	50	50	
Non-fibroid uterine volume	39% decrease	37% decrease	N.S.
Fibroid uterine volume	70% decrease	39% decrease	<0.05

Fig. 2 The effect of GnRH-agonist plus raloxifene versus GnRH-agonist alone on uterine volume and leiomyoma volume. Data from Palomba et al. 2002b

et al. 2001). However, in premenopausal women, this dose was ineffective; doses as high as 180 mg daily were required to even see a marginal response in some women (Palomba et al. 2002a). It appears that raloxifene is capable of blocking the effect of estrogen on fibroids when levels are relatively low, but when premenopausal levels are present the blockade is ineffective.

The conflicting data from pre-and postmenopausal women led to the notion that raloxifene might be efficacious if premenopausal women could be "converted" via a medical menopause. Palomba and colleagues combined raloxifene with GnRH agonist treatment in an attempt to do just that (Palomba et al. 2002b). A randomized trial comparing GnRH agonist plus raloxifene 60 mg daily versus GnRH agonist plus placebo demonstrated that after 6 months substantially more fibroid volume reduction was seen with combination therapy than the control arm (Fig. 2). The size reduction remained stable for an additional 12 months of treatment, and myoma symptoms also remained improved (Palomba et al. 2004). The primary side effect, as expected, was hot flashes, but endometrium remained atrophic and there was no significant decrease in bone mineral density. Thus, the combination therapy proved superior in fibroid treatment to either drug alone, and also ameliorated a major adverse effect of GnRH agonists by protecting bone density. This regimen may prove to replace solo GnRH agonist therapy when medical therapy is desirable.

6 Aromatase Inhibitors

Aromatase inhibitors are molecules that directly inhibit estrogen synthesis by either blocking or inactivating aromatase, the enzyme responsible for synthesizing estrogens from androgen precursors. While estrogen is principally produced in the ovary premenopausally, the aromatase enzyme can be found elsewhere, such as in adipose tissue and endometriosis. Aromatase is also produced in many fibroids, which may explain why some tumors do not regress in hypoestrogenic states (Ishikawa et al. 2009).

Given the above facts, it would be anticipated that aromatase inhibitors would be of value in pre- and postmenopausal women. Side effects in such patients would be those expected in a hypoestrogenic state: Hot flashes, vaginal dryness, and bone loss. However, the utility in women with functioning ovaries might be expected to be poor, in that a hypoestrogenic state would likely stimulate the hypothalamic-pituitary-ovarian axis, with greater levels of FSH production, and resultant follicular development; such developing follicles would be unable to ovulate due to an absent LH surge (as estrogen, the surge trigger, is low) and ovarian cysts would result.

Data are limited for the use of these agents in the treatment of fibroids. Most publications are case reports or small uncontrolled series. However, there is currently one randomized trial comparing the aromatase inhibitor letrozole 2.5 mg/day to GnRH agonist in the treatment of uterine fibroids (Parsanezhad et al. 2010). In this study, premenopausal women with a single fibroid >5 cm in diameter were treated for 12 weeks. The patients treated with letrozole had 45 % reduction of volume of the fibroid, a result that did not differ from the GnRH agonist group. However, the patients treated with letrozole had a more rapid onset of size reduction, saw no changes in steroid hormone or gonadotropin levels, and also had no development of ovarian cysts. The long-term or preoperative use of their medication may well prove superior to the existing medications.

7 Progesterone Receptor Modulators

As progesterone has been shown to be critical to the growth of fibroids, a logical pharmaceutical approach to the treatment would be better to inhibit the action of progesterone on these tumors. Progesterone receptor modulators are a class of compounds that interfere with the progesterone–progesterone receptor interaction. Two types of such inhibitors have been developed: (1) the pure progesterone receptor antagonist, and (2) the selective progesterone receptor modulator, which has either agonist or antagonist activity depending upon the site of action.

7.1 Progesterone Antagonists

Mifepristone is a progesterone receptor antagonist with little or no agonist activity. It binds to the progesterone

receptor with high affinity, and also binds to the androgen and glucocorticoid receptors. The drug has been shown to reduce the progesterone receptor number in fibroids (Bouchard et al. 2011).

Side effects of this medication include vasomotor symptoms, nausea, and fatigue, but all are relatively infrequent. High doses can produce anti-glucocorticoid effects, and thus have been avoided in recent trials. The most concerning adverse effect is the effect of the drug on the endometrium. The inhibition of progesterone action on the endometrium creates a milleu of pure estrogen stimulation, resulting in histologic changes resembling hyperplasia. This was noted in 28 % in one of the original studies (Steinauer et al. 2004), although re-evaluation of the biopsies later reduced this rate to 14 % (Eisenger et al. 2003). Nevertheless, this finding raises concern for the value of progesterone antagonists in the long-term treatment of uterine fibroids.

Mifepristone has been shown to reduce fibroid volume consistently, by around 50 % in most studies with a dosage range of 5–50 mg/day (Steinauer et al. 2004). The studies also report a high rate of symptom relief (up to 75 %) and a 91 % rate of amenorrhea. Recently, a randomized trial comparing 5 and 10 mg daily doses for 6 months again demonstrated significant volume reduction, but also found that 1-year posttreatment in the majority of women remained asymptomatic (Esteve et al. 2012). Also interesting is an open-label study of the utility of 2.5 mg mifepristone daily. While the uterine volume was reduced only 11 % over the 6-month trial, the improvement in quality of life was similar to that seen with higher doses (Eisinger et al. 2009). This raises the possibility that effective medical treatment may not hinge upon reducing fibroid size in many women.

Ulipristal is a pure progesterone antagonist with no agonist activity. It binds progesterone receptors, but not estrogen receptors, and has less antiglucocorticoid activity than mifepristone (Hild et al. 2000; Attardi et al. 2000, 2002). The drug has been shown to reduce progesterone receptors, and downregulate growth factors and their receptors in cultured leiomyoma cells (Wang et al. 2006; Xu et al. 2006).

The side effect profile of ulipristal shows it to be extremely well tolerated. Estrogen levels are maintained in the mid-follicular range, and thus vasomotor symptoms are infrequent and less profound. There is no evidence of effect upon bone mineral density, and anti-glucocorticoid effects seem to be rare. The effect on the endometrium, a major concern for these medications, has been thoroughly investigated. Over 60 % of women treated with ulipristal show changes typical of this class of drugs after 3 months: Glandular dilatation and dyssynchronous glands and stroma. However, these changes resolved after a 6-month drug-free period (Donnez et al. 2012a). This leads to the intriguing possibility that intermittent therapy might eliminate the concerns of endometrial hyperplasia with this medication.

A number of small studies had previously suggested the value of ulipristal in the treatment of myomas, but two recent randomized clinical trials highlighted the value of this drug. In one, a randomized trial compared ulipristal 5 and 10 mg daily to placebo preoperatively in women with anemia (Donnez et al. 2012b). Bleeding was controlled in over 90 % of those treated with active medication, and there was a significant (but small) decrease in fibroid volume. A second trial compared ulipristal to a GnRH agonist. Compared to the GnRH agonist, ulipristal-induced amenorrhea more rapidly and produced a greater increase in hemoglobin levels in treated patients. While GnRH agonist produced a greater size reduction in the fibroids, the effect of ulipristal appeared to be more sustained. This had been suggested in prior studies (Eisenger et al. 2005).

Thus, ulipristal appears to be a drug worthy of consideration in the preoperative treatment of uterine fibroids; furthermore, its value as a long-term medical treatment via intermittent use is conceivable, and is in need of investigation.

7.2 Selective Progesterone Receptor Modulators

As stated earlier, some progesterone receptor antagonists have agonistic properties in some tissues, organs, or hormonal milleus. These medications are termed selective progesterone receptor modulators, or SPRMs. The most intensely investigated of this class is asoprisnil. This medication exhibits a mixture of agonist and antagonist actions, with a high degree of uterine selectivity. It induces amenorrhea and suppresses endometrial growth (Chwalisz et al. 2006). In addition, it has no antigluticorticoid effects. In culture, asoprisnil produces an anti-proliferative effect upon cultured leiomyoma cells (Chen et al. 2006).

Phase 1 trials with asoprisnil demonstrated reversible suppression of menstruation. Phase 2 trials showed, via multicenter randomized trials, that the drug reduced fibroid size by 36 % and menorrhagia in a dose-dependent manner, with an amenorrhea rate of up to 83 % with a dose of 25 mg daily (Chwalisz et al. 2007). The drug has also been shown to reduce uterine artery blood flow (Wilkens et al. 2008).

Asoprisnil appeared to have relatively few and mild side effects in the above-mentioned trials; however, endometrial histologic changes were seen typical of progesterone

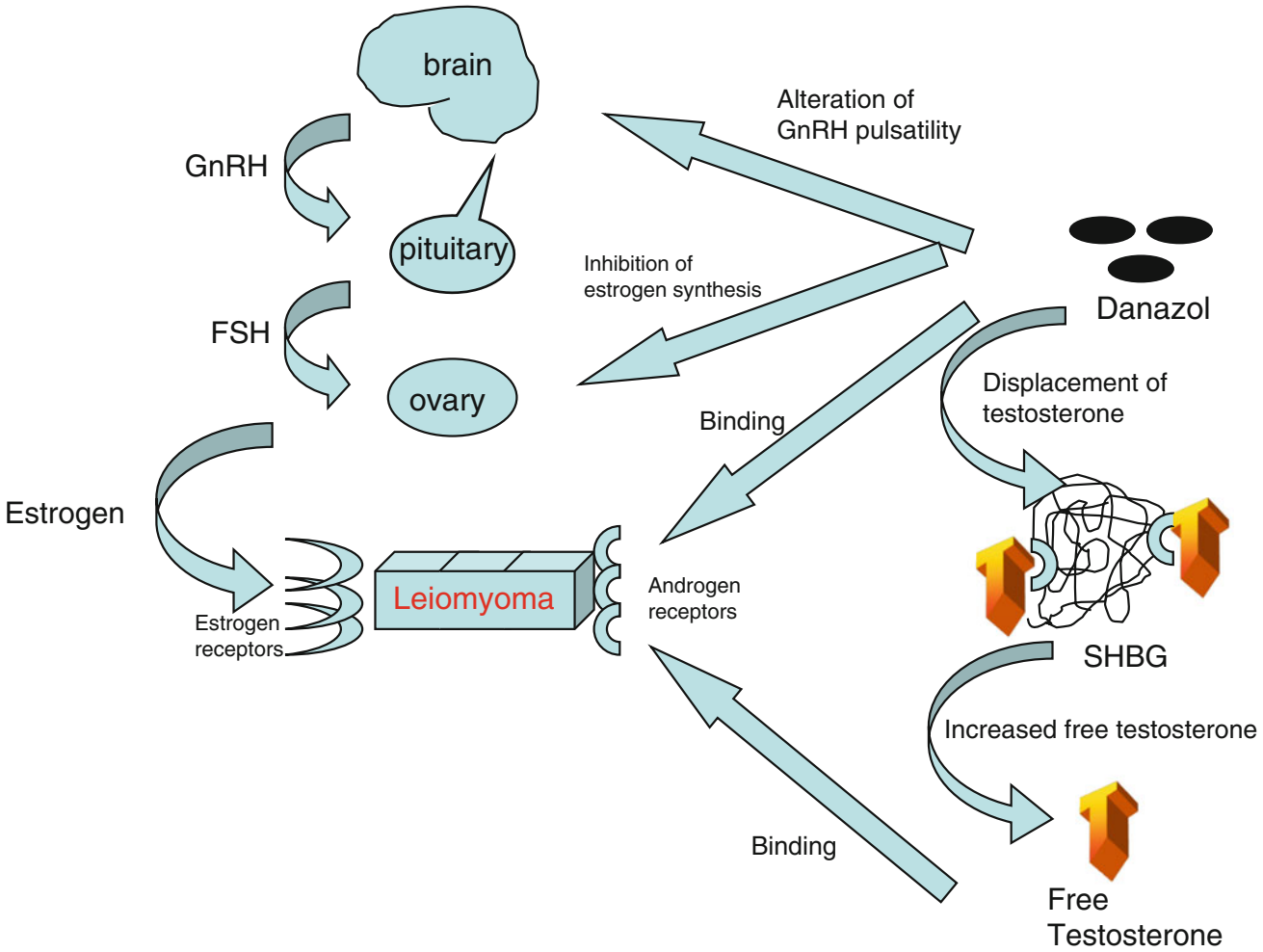

Fig. 3 Mechanism of action of danazol upon uterine fibroids

receptor antagonists. As a result, phase 3 trials of the drug were abandoned despite the encouraging results.

8 Other Available Therapies

8.1 Danazol

Danazol is an isoxazole derivative of 17-alpha-ethinyltestosterone, and functions in a number of different ways that may inhibit the growth and maintenance of uterine fibroids. The drug alters GnRH pulsatility, resulting in ovulation dysfunction (Panidis et al. 1994), and also creates hypoestrogenemia by inhibiting multiple enzymes in the steroidogenic pathway, including aromatase (Barbieri and Ryan 1981; Ishihara et al. 2003) (Fig. 3). Furthermore, by binding to SHBG, testosterone is displaced and the amount of free testosterone rises. This combination of anti-estrogenic, anti-progestogenic, and androgenic effects seems to be beneficial in reducing fibroid size. Additionally, danazol appears to increase the uterine artery impedance to blood flow.

Clinical studies suggest that the medication is efficacious while being administered, and perhaps for a period of time thereafter. Danazol 400 mg/day produced a 24 % decrease in uterine volume by 4 months; the size was still significantly reduced 6 months after discontinuation of treatment. Symptom reduction was noted in all women treated (De Leo et al. 1999). A lower, more tolerable dose of the androgen has also been tried; women were treated with 100 mg daily for 6 months resulting in a mean myoma volume decrease of 38 % (La Marca et al. 2003).

Unfortunately, danazol has multiple androgenic side effects such as weight gain, acne, inappropriate body hair growth, oily skin, and decreased breast size. These and other less frequent symptoms may be reduced or eliminated, however, with lower doses of the drug, and trials of 50–100 mg daily for extended lengths of time are currently being planned.

8.2 Cabergoline

The dopamine agonist cabergoline has also been trialed in an attempt to medically treat myomas. The drug is believed to produce its effect via decreased uterine artery blood flow. In randomized trails against a GnRH agonist, this drug appears to cause comparable shrinkage of the tumors with few side effects (Melli et al. 2007; Sayyah-Melli et al. 2009). Further studies are definitely needed to better evaluate the potential usefulness of this drug in the long-term medical treatment of fibroids.

8.3 Gestrinone

Gestrinone is another androgenic steroid used to treat myomas. Like danazol, the medication is anti-estrogenic and anti-progestogenic. Studies suggest that the drug reduces uterine volume up to 40 % with 6 months of usage (Coutinho et al. 1986; Coutinho and Goncalves 1989). Of interest is that the treatment effect appears to be fairly durable, with a persistence in volume decline lasting for 18 months (Coutinho and Goncalves 1989).

8.4 Oral Contraceptives

Many publications have stated that estrogen–progestogen oral contraceptives are contraindicated in women with uterine fibroids; this conclusion is based upon in vitro studies of both hormones acting as stimulants for growth of myoma cells. There are very limited data regarding the clinical applicability of this conclusion, however. Oral contraceptives are associated with a decrease in duration of menstrual flow, and in at least one small study there was no associated change in myoma size (Friedman and Thomas 1995). This is not the case, however, with pure progestin therapy, as several studies have documented this class of medications when given alone will in fact cause tumor growth (Harrison-Woolrych and Robinson 1995).

8.5 Ascorbic acid

Ascorbic acid, also known as vitamin C, has a known role in tissue repair, as well as in platelet activation and aggregation. It has been proposed that many patients may have suboptimal levels of vitamin C producing a propensity to have greater blood loss during and after surgery. This has been tested in a randomized trial of patients undergoing abdominal myomectomy, where intravenous administration during and after surgery reduces blood loss, duration of surgery, and days of hospitalization (Pourmatroud et al. 2012).

9 Experimental Therapies

In addition to the above-mentioned medications, there are numerous agents in the early stages of investigation which may hold promise in the medical treatment of fibroids.

Catechol-O-methyl transferase (COMT) catalyzes the conversion of hydroxylated estrogen metabolites into their methylated forms. 2-hydroxyestradiol, a substrate for COMT, acts as an anti-estrogen in the body. Fibroids are known to have high levels of COMT and thus are able to eliminate 2-hydroxyestradiol from the local environment, promoting the growth stimulating effect of estradiol. It has been theorized that inhibition of COMT will result in a decrease in the estrogen effect upon fibroids, possibly resulting in tumor shrinkage. This hypothesis has been tested in the Eker rat model, a species that spontaneously produces uterine fibroids. Ro 41–0960, a COMT inhibitor, produced a dramatic reduction in fibroid volumes in Eker rats over 4 weeks (Hasson et al. 2011). However, contradictory data are provided by studies utilizing the COMT product 2-methoxyestradiol, which has also been shown to decrease leiomyoma cell proliferation in culture (Salama et al. 2006). Further studies are clearly needed to determine the validity of this approach in the human.

As stated earlier, epidermal growth factor (EGF) seems to play a role in fibroid growth. Selective inhibitors of the EGF receptor have been studied for their effect upon fibroids, with positive results. AG1478 and TKS050, two such receptor inhibitors, have been shown in vitro to block leiomyoma cell growth (Shushan et al. 2004, 2007).

Genestein, a naturally occurring phytoestrogen and known tyrosine kinase inhibitor and activator of PPAR gamma, also has been shown in multiple studies to inhibit leiomyoma cell growth. The mechanism is as yet unclear (Shushan et al. 2007; Miyake et al. 2009).

Halofuginone is an antifibrotic drug that inhibits collagen type 1 production, TGF betaI signaling, and cell proliferation in mesenchymal cells. When tested on leiomyoma cells in culture, the medication inhibited cell proliferation by inducing apoptosis, reducing collagen production, and reducing TGF levels (Grudzien et al. 2010).

Circumin is an active component of the spice Turmeric (Curcuma longa), and has been used for many years as a natural food supplement. This medicine suppresses the growth of several tumor cell lines in vitro, including uterine leiomyoma cells (Malik et al. 2009; Tsuiji et al. 2011). The mechanism seems to be through activation of PPAR gamma and alteration of the cell cycle. Investigation into this herbal

agent as a possible inhibitor of fibroid development and growth is needed, both in vitro and epidemiologically.

The Chinese herbal component Isoliquiritigenin is often touted as having anticarcinogenic properties. It is highly prevalent in licorice. In vitro, this drug inhibits myoma cell proliferation by initiating apoptosis through downregulation of Bcl-2 and other apoptosis inhibitors (Kim et al. 2008).

Interferon alpha, an anti-angiogenic cytokine, has been shown to inhibit leiomyoma cell growth in culture, as well as that of myometrial cells and endometrial stromal cells.

Pioglitazone, an insulin-sensitizing agent, acts through the PPAR gamma receptor to leiomyoma cell growth in vitro in a dose-dependant manner (Loy et al. 2005).

In summary, there are a variety of novel approaches being applied to the issue of limiting fibroid proliferation and/or producing a reduction in size. While many of these pathways look promising in the laboratory, more advanced investigation is needed prior to generating a significant level of enthusiasm for these medications.

10 Conclusions

It is astounding that the most common tumor in women, the uterine fibroid, to date has no widely accepted form of medical treatment. Nevertheless, the large number of forays into development of such an intervention have resulted in a number of medications of demonstrable value. Preoperative therapy is clearly of benefit in the anemic patient undergoing hysterectomy or myomectomy; the utility in the nonanemic patient is less clear.

Long-term therapy to avoid or significantly delay surgery is the remaining question mark for the medical approach to this disease. A number of drugs appear to have the potential to be used in this manner, but appropriately crafted long-term studies are sorely needed. Such investigations will not only need to determine the effect on fibroid volume and symptoms, but also side effects over time, quality of life measures, and cost-effectiveness. Approaches may include individual therapies, combinations (such as GnRH agonists with add-back hormonal therapy or GnRH agonist with raloxifene), and intermittent therapy.

More importantly, as our knowledge of fibroid growth, development, and maintenance increases, so does our collection of potential therapeutic targets. The development of highly specialized molecules to attack specific targets involved in an increasingly complex fibroid growth pathway will add substantially to our future capacity to control these tumors in a nonsurgical manner.

The treatment of uterine fibroids is, today, primarily surgical or via interventional radiology. However, the future lies in medical therapy. So let the surgeon beware: if you enjoy operating on uterine fibroids take advantage of your current opportunities, as your time may be limited!

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