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Concurrent use of daily subcutaneous leuprolide and daily oral MPA versus leuprolide alone has demonstrated that only isolated leuprolide was associated with significant uterine volume reduction, whereas the combined group showed a reduction of only 14% after 6 months.[37] Conversely, there was a significant decrease in the incidence of hot flashes in the group that used combined MPA. Tibolone 2.5 mg has also been studied as add back therapy and it seems to be an effective option, since there was relief of hot flashes, lower bone loss and no decrease in treatment efficacy.[38] Other medications were also tested in small RCTs, such as progesterone, with indifferent results, raloxifen and combined estrogen-progesterones, with reduced bone loss.[7]

GnRH antagonists

Differently from GnRH agonists, these drugs are not routinely used for the treatment of UF. The rationale for studying them was that the absence of an initial flare-up effect would lead to a more rapid decrease in uterine volume compared to GnRH-a. A randomized trial studied the effect of cetrorelix, a GnRH antagonist, versus placebo for 4 weeks prior to surgical treatment in 109 women, demonstrating a significant reduction in tumor volume (42.3% vs. 11.1%).[39] A smaller, open-label study including only 19 patients reported on the efficacy of ganirelix, another GnRH antagonist, in decreasing tumor volumes and demonstrated a significant reduction in a median of 19 days.[40] No trials assessing GnRH antagonists as long-term medical treatments for fibroids were located and pre-operative use still lacks high quality evidence.

SPRM

SPRM are structurally similar to mifepristone, but have both agonist and antagonist actions. The two main drugs in this class are asoprisnil and ulipristal, with the latter already approved for pre-operative use in some countries. A randomized, multi-center trial including 129 women has demonstrated significant control of AUB after 12 weeks of treatment with asoprisnil, with improvements in 28-83% of the participants, according to the employed dose (5-25 mg, with the latter being the most effective). Fibroid volumes also decreased by 36%, and reported hypoestrogenic symptoms were minimal.[41] Ulipristal has been studied in a non-inferiority trial involving 307 women compared to leuprolide, a GnRH-a, in 5 mg and 10 mg dosages – a study titled PEARL II trial. After 3 months, there was an improvement in uterine bleeding in 90% of the 5 mg group, 98% of the 10 mg group and 89% of the leuprolide group. Fibroid volumes decreased by 36%, 42% and 53% in the three groups, respectively.[42] The same research group also compared ulipristal with placebo for pre-operative treatment of women with UF in the PEARL I trial. They reported effective control of uterine bleeding in 91% of the women receiving 5 mg and in 92% of those receiving 10 mg, versus 19% of those receiving placebo. Fibroid volumes also decreased up to 21%.[43] Both PEARL trials led to the approval of ulipristal in the European Union as a pre-operative treatment of moderate to severe symptoms associated with UF. Long-term safety, however, is controversial for this class of drugs. In the PEARL II trial, only one woman, among 200 who received the medication, developed simple endometrial hyperplasia, but up to 59% of those who received ulipristal developed non-physiologic endometrial findings that appear to be specifically associated with the action of SPRMs,[44] compared to 12% of those who received leuprolide.[42] Another study with ulipristal, which enrolled 546 women, did not report any endometrial changes.[45]

Along with the antiprogesterones, SPRMs are potentially effective medical treatments for fibroids. Safety concerns over prolonged use, however, exist and long term endometrial safety still needs to be ascertained before these agents can be employed as exclusively medical treatments. Pre-operative use, however, has been recognized as safe and effective.

Selective estrogen receptor modulators

These molecules have agonist-antagonist activity on estrogen receptors (ER), with different actions across various estrogen-sensitive tissues. The main agents in this class are tamoxifen, frequently used in the treatment of breast cancer, and raloxifen, used as an antiresorptive drug in the treatment of osteoporosis. They have sparked interest in the treatment of leiomyoma due to their anti-estrogen potential. Tamoxifen has an agonist action on endometrial ERs and carries the risk of leading to endometrial pathology. Also, there are reports of significant leiomyoma growth in women with fibroids who used the drug for breast cancer treatment.[46] Raloxifen, on the other hand, has a more favorable profile, and a randomized clinical trial including 70 women with fibroids has shown volume reductions of 40% for up to 1 year of follow-up with the use of 60 mg daily. The study, however, only enrolled women who were postmenopausal, and it is not known whether this efficacy is maintained in premenopausal women.[47] There is no high quality evidence regarding the use of SERMS for treating fibroids.

Aromatase inhibitors

These agents suppress the activity of the enzyme aromatase, responsible for the conversion of androgens into estrogens. It has been observed that UF cells may carry an intrinsic capacity of secreting estrogens due to the expression of aromatase, leading to the experimental use of this class of drugs in the treatment of UF. A randomized trial involving 60 premenopausal women with fibroids, comparing letrozole, an aromatase inhibitor, with triptorelin, a GnRH-a, has demonstrated significant decreases in tumor volumes for both drugs (45% vs. 33%).[48] No patient in the letrozole group, however, complained of hot flashes, while 96% in the GnRH-a group did. Another clinical trial, an open-label study involving 20 women with fibroids, studied the action of anastrozole on uterine volumes and on complaints of uterine bleeding

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and dysmenorrhea, demonstrating a 9.3% volume reduction and a significant decrease in referred symptoms.[49] A study evaluating the effects of anastrozole over fibroid volumes and blood flow has also demonstrated a decrease in the volume of the tumors (40.9% reduction, $P < 0.01$), but has shown no differences in Doppler parameters, suggesting a non-vascular mechanism of action for tumor volume reduction.[50] More robust evidence regarding the efficacy and safety of this class of drugs is still needed before they can be widely employed.

Danazol

Danazol is a synthetic steroid, structurally similar to testosterone, which has an inhibitory action over sex-steroids synthesis and directly inhibits the progesterone receptor. It was more frequently used in the treatment of endometriosis, but its efficacy in the treatment of UF was assessed by some studies. A small study involving 20 women has demonstrated significant tumor volume reduction (23.6% ± 5%) and partial to complete symptomatic improvement, which persisted after 6 months of treatment withdrawal.[51] Higher quality studies, however, are lacking, and a systematic review from the Cochrane Collaboration could not find any RCTs that supported the efficacy of this treatment.[52] Besides, Danazol has significant adverse effects due to its androgenic action, including weight gain, acne and hirsutism.[53]

Gestrinone

Gestrinone is a steroid with antiestrogenic and antiprogestogenic action, also used in the treatment of endometriosis. It has been studied for the treatment of UF in the past, with up to 60% reductions in fibroid volumes.[54] A more recently published, open-label study, which enrolled 16 women, has demonstrated amenorrhea in 69% of the participants after 6 months of treatment, together with tumor volume reductions of 32% ± 10.8%. As is the case for danazol, there is very little robust evidence to support the use of gestrinone in the treatment of fibroids.

Conclusions

Treatment of UF must be individualized. A great proportion of women will be diagnosed with fibroids when seeking medical care for other complaints or when performing imaging studies for other indications. These women must be counseled on the characteristics of the disease, especially those who are asymptomatic. For women seeking treatment because of UF-related complaints, the nature and characteristics of the symptoms, the patient's age and the desire for future fertility must all be taken into account during treatment counseling. Fibroid volume, by itself, must not be considered an indication for surgical intervention and asymptomatic women may need nothing more than regular reevaluation. Large fibroids, however, deserve attention, especially if rapid growth has occurred. There is no consensus on whether patients with large and rapidly growing nodules should always receive surgical treatment, despite the absence of symptoms. Imaging techniques and LDH dosage may assist in decision-making.

GnRH-a are the most effective medications to improve symptoms and decrease tumor volumes, but side effects and a maximum length of safe use limit their clinical application. Strategies involving long-term use of GnRH-a with add-back therapy may be offered to patients with good responses to avoid a surgical intervention. There is limited evidence on the effect of COCs and progestagens, but published studies have shown slightly reduced uterine volumes and improved bleeding patterns. These drugs may be an interesting initial choice due to their potential benefit, low cost and relative safety. LNG-IUS may be offered as an effective option for managing bleeding in women with non-submucosal fibroids. Short term use of SPRMs is safe and ulipristal has already been approved for pre-operative treatment of UF in some locations. Long term use of SPRMs and antiprogestogens both show promising results as effective long-term medical treatments for fibroids. Endometrial safety after prolonged use, however, is still a concern for these agents. Experimental therapies, such as aromatase inhibitors and SERMS, still have little applicability in the clinical setting.

Pharmacological treatment of UF should always be considered when counseling women on the potential strategies for addressing fibroid-related complaints. Many women will prefer long-term medication use over some form of invasive treatment. Published evidence supports the efficacy of many agents for symptomatic control and a trial of medical treatment in selected and motivated patients may obviate the need for surgery.

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