Update on Management of Uterine Fibroid

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Uterine fibroid is a slowly growing benign smooth muscle tumor. Approximately 25% of women after the age of 35 years harbor uterine fibroid. Most of these women are asymptomatic and in general, they do not need any treatment.

For those with symptomatic uterine fibroid, several treatment options are available. The type of treatment depends on the age, desire for future fertility, previous obstetrical performance, and location and the size of the myoma.

Medical Therapy
Medical therapy avoids complications associated with surgery and permits uterine preservation. However, symptoms usually recur after discontinuation of therapy. Medical treatment is used mainly for temporary control of symptoms, and for preoperative management. The purpose is to reduce the size of the fibroid and improve the hematological status of the patient. Several medications are available.

Oral contraceptives
Combined oral contraceptive pills and progesterone-only pills are effective for the treatment of abnormal uterine bleeding but not for uterine fibroids. Furthermore, estrogen and progesterone may promote the growth of uterine myoma.

Long acting progesterone
Administration of medroxyprogesterone acetate (Depo Provera, 150 mg/month) for 6 months decreased uterine bleeding in 30-70% of patients. The volume of the fibroid also reduced. However, the effect is temporary and it is not as effective as gonadotropin-releasing hormone agonists (GnRHa).

Levonorgestrel-releasing intrauterine contraceptive device (IUD)
This is a new type of medicated IUD. The addition of L-norgestrel to the IUD is associated with a reduction in the amount and duration of menstrual blood loss. It is an effective treatment for dysfunctional uterine bleeding. However, those with intrauterine lesion such as submucous fibroid or with uterine size of >12 weeks gestational size are not good candidates. Furthermore, the IUD expulsion rate in these patients is high (12%).

Antiprogestin (mifepristone, RU 486)
Mifepristone (RU486) is a derivative of norethindrone that has both antiprogesterone and antiglucocorticoid activities. In the endometrium, it exerts an antiestrogenic effect. Morales et al reported that mifepristone (25 mg daily for 3 months) resulted in 50% decrease in the size of uterine myoma. Compared to GnRHa, its use is associated with less hypoestrogenic side effects.

Selective Progesterone Receptor Modulator (SPRM)
SPRM is a new class of progesterone receptor modulators. They exert tissue-selective progesterone agonist, antagonist, or mixed agonist/antagonist effects on various tissues including the endometrium. Preliminary study with SPRM showed that it reduced the duration and amount of uterine bleeding in a dose-dependent manner.
Selective estrogen receptor modulator (SERM)
Raloxifene is one of the SERMs that have been evaluated in women with uterine fibroids. In postmenopausal women, it reduces the volume of the fibroid. However, due to the spontaneous shrinkage in myoma after menopause, it might not be relevant clinically.

Aromatase inhibitors
Aromatase inhibitors inhibit the conversion of androgen to estrogen. In theory, the reduction in estrogen level might be beneficial for uterine fibroid. Bulun et al administered aromatase inhibitor, fadrozole to a woman with urinary retention secondary to a large fibroid. The fibroid volume decreased 71% in 8 weeks.

Gestrinone
Gestrinone is a derivative of ethynyl-nor-testosterone with antiestrogen and antiprogesterone properties. A few studies have shown that gestrinone treatment leads to a reduction in uterine fibroid of up to 40%. Unfortunately, it is associated with significant androgenic side effects.

Androgenic steroids (Danazol)
Danazol is an isoxazole derivative of 17-alpha-ethinyl testosterone (ethisterone). It has multiple effects at different levels of the hypothalamic-pituitary-ovarian axis by binding to intracellular steroid receptors for androgens, progesterone, and glucocorticoids. It reduces the volume of fibroids (average 23.6%) and improves uterine bleeding. However, its use is limited by the side effects of acne, hirsutism, and weight gain.

GnRHa
GnRHa is the most effective and widely used medical treatment of uterine myomas. It causes a hypoestrogenic state leading to 35% shrinkage of the myoma and 61% decreased in uterine volume. Uterine bleeding decreases. Obese women show less diminution in uterine volume, probably because of the availability of extragonadal estradiol.

As other medical treatments in reproductive aged women, the uterine size gradually returns to its pretreatment size following discontinuation of GnRHa. Its use in perimenopausal women is more advantageous. It is hoped that during or immediately after GnRHa treatment, natural menopause ensues, thus reducing the probability of myoma regrowth.

For preoperative treatment before laparoscopic myomectomy or hysterectomy, most surgeons will use a 3-month course of GnRHa. Reduction in the size of myoma and decreased in its vascularity facilitates the procedure. Prior to hysteroscopic procedure, a single dose of GnRHa is usually given 4 weeks before the procedure. Side effects of GnRHa are hot flashes, vaginal dryness, headaches, depression, hair loss, and musculoskeletal stiffness and discomfort. A slight decrease in bone mineral density can occur after long-term treatment of > 6 months.

Gonadotropin-releasing hormone antagonist (GnRHag)
GnRHag acts by competitive binding of the GnRH receptors. Unlike GnRHa, its treatment is not associated with an initial “flare-up” phenomenon. This leads to a faster effect than that with GnRHa. In spite of this advantage, GnRHag is not widely used for uterine fibroid due to the requirement of daily treatment. If longer-acting GnRHag becomes available, preoperative treatment with GnRHag would be preferable.

Radiologic Therapy

Uterine Fibroid Embolization (UFE)
UFE has become one of the main treatments of uterine fibroid. Two important studies were published in the past year regarding UAE. The first study is a prospective, randomized trial of UAE comparing women offered a choice of UAE or hysterectomy versus hysterectomy only. Fifty-seven patients were randomized. The complication rates of the two treatments were similar. Patients underwent UAE resumed normal activity faster than after hysterectomy, but satisfaction rate was
higher with hysterectomy (88%) than with UAE (78%). The second study is a longitudinal multicenter trial of 538 women who were followed prospectively (18-19). The reduction in the volume of the dominant fibroid was 42%, and in symptoms was 77-86%. Patient’s satisfaction rate at 3 months follow-up was 91%. Of all participating women, 3% subsequently underwent a hysterectomy within 8 months following UAE

Magnetic Resonance Imaging (MRI) Guided Focused Ultrasound

One the newest technique to treat uterine fibroid is the use of a high intensity focused ultrasound (HIFU). Volume reduction with this treatment is small and recurrence rate is high. In addition, the treatment is associated with side effects including full thickness burns of the abdominal wall.

MRI-directed cryotherapy

Another MR-controlled treatment of fibroid is MRI-directed cryotherapy. Initial report revealed a 65% volume reduction. Further efficacy and safety studies for these two MR controlled treatments are needed.

Surgical Therapy

Surgery is the conventional treatment of uterine fibroid. Indications for surgery include persistent abnormal uterine bleeding, pelvic pain, pressure symptoms, and rapidly enlarging fibroid. Surgery may also be indicated for treatment of fibroid-related infertility and recurrent pregnancy loss.

Myomectomy

The standard surgical treatment for women who wish to retain their fertility is myomectomy. Submucous myomectomy is performed by hysteroscopy, whereas intramural or subserous myoma by laparoscopy or laparotomy.

Laparoscopic Myolysis

Myoma coagulation or myolysis has been advocated. However, this treatment is associated with adhesion formation and possible uterine rupture in pregnancy. Most gynecologists have abandoned myolysis.

Laparoscopic Uterine Artery Occlusion

Realizing the efficacy of UFE, gynecologists have started to occlude the uterine arteries as well. In one report, the authors performed laparoscopic bilateral uterine artery occlusion in eight patients with uterine fibroid. The patients experienced decreased uterine bleeding and less pressure symptoms. Unlike UFE, laparoscopy is a surgical procedure. Its efficacy and cost-effectiveness remains to be seen.

Hysterectomy

Hysterectomy is a definitive treatment of uterine fibroid and advanced-laparoscopic surgeons perform hysterectomy by laparoscopy. Many studies have shown the safety and efficacy of laparoscopic hysterectomy. It could be performed in an outpatient setting with reduced hospital costs. However, laparoscopic hysterectomy requires special skills and training.
Controversy

Uterine Fibroid and Infertility

Among infertile women especially among those with unexplained infertility, fibroid found incidentally is often regarded as a cause of infertility. It has been postulated that fibroid may cause infertility by mechanical means; it may alter normal transport of gametes or embryos through the genital tract. In addition, it may alter the normal pattern of uterine contractility and uterine receptivity.

Clearly, submucous fibroids or large intramural fibroids that cause distortion of the uterine cavity reduce fertility and the fertility improves after myomectomy. All types of myomectomy (laparoscopy, laparotomy, or hysteroscopy) increased the pregnancy rates. However, in a large meta-analysis, Pritts et al showed that the relative risk for pregnancy in women with intramural fibroids undergoing in-vitro fertilization (IVF) treatment compared to women without fibroids was 0.94, which hardly supports the idea that these fibroids play a negative role. Fertility enhancing effects of removal of intramural fibroids remains unclear.

References:


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