MEDICAL TREATMENT FOR UTERINE MYOMAS

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SUMMARY

Uterine myomas are the most common benign tumors in the female reproductive tract. Most women with myomas are asymptomatic. Therefore, expectant observation and follow-up are often recommended for these myoma patients. However, myomas may cause menstrual symptoms, pelvic pain, pressure complaints, subfertility or pregnancy-related complications, with resultant requests for a definitive treatment. The management of myomas has become multidisciplinary in the past 20 years. Basically, the choice of treatment depends on the patient's age, the reason for treatment, the issue of fertility preservation, and the patient's preference. The treatment spectrum includes an expectant management, medical therapy, surgical intervention, uterine artery embolization or ablative techniques. Medical therapy is an option for women with symptomatic myomas who prefer non-surgical treatment, consider fertility preservation, or expect a less aggressive operation after shrinkage of the uterine volume. This review will summarize the recent well-documented drugs for the management of uterine myomas. [*Taiwan J Obstet Gynecol* 2008;47(1):18–23]

Key Words: medical therapy, uterine myomas

Introduction

Uterine myomas (called "myomas") are the most common benign tumors in the female reproductive tract, with an incidence ranging from 5.4% to 77% [1,2], and without the threat of mortality and with little influence on morbidity [3]. The precise etiology of myomas has not been well elucidated, but it is assumed to be closely related to hormonal exposures, the promotion of growth factors or genetic changes [4]. Based on clinical observation and epidemiologic data, myomas develop and grow during the reproductive years and regress after menopause, indicating the critical role of estrogen in the pathogenesis of myomas. The use of estrogen agonists or postmenopausal hormone therapy appears to increase the incidence of myomas [5], suggesting that sex hormones may play key factors in the pathogenesis of myomas.

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Accepted: December 14, 2007

The following findings support the important role of sex hormones in the development of myoma: (1) rare occurrence before puberty but most prevalent during the reproductive years, and regressing after menopause; (2) increased incidence by factors such as obesity and early menarche that increase overall lifetime exposure to estrogen; and (3) difference in sex hormone receptor concentrations between the normal myometrium and uterine myoma [6,7]. Besides the role of estrogen in the pathogenesis of uterine myomas, progesterone may be also a key factor. The inconsistencies in the clinical effects of progesterone on myomas may be explained by dual actions on the growth of uterine myomas in several *in vivo* studies. Progesterone stimulates the proliferation of myoma cells by inducing the epidermal growth factor [8], upregulating antiapoptotic protein Bcl-2 expression [9], and decreasing tumor necrosis factor-α expression [10]. On the other hand, progesterone inhibits myoma growth via downregulation of insulin-like growth factor-I expression [11]. Since sex hormones and sex hormone receptors are involved in the pathogenesis of myomas, the underlying mechanism of almost all medical therapy is based on the blockage of the receptor mechanism in myomas. Currently available and well-accepted medical treatments for myomas

should be classified as non-hormonal treatment or hormonal treatment.

Medical Treatment

Most women with myomas are asymptomatic. Therefore, expectant observation and follow-up are often recommended for these myoma patients. However, myomas may cause menstrual symptoms, pelvic pain, pressure complaints, subfertility or pregnancy-related complications, and a rare threatening condition, with resultant requests for a definitive treatment [12–18].

The management of myomas has become multidisciplinary in the past 20 years. Basically, the choice of treatment depends on the patient's age, the reason for treatment, the issue of fertility preservation, and the patient's preference. The treatment spectrum includes an expectant management, medical therapy, surgical intervention, uterine artery embolization or ablative techniques [19–22]. Medical therapy is an option for women with symptomatic myomas who prefer non-surgical treatment, consider fertility preservation, or expect a less aggressive operation after shrinkage of the uterine volume.

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs are a main part of non-hormonal therapy for myomas, although their efficacy has not been proved [19]. The main hormone therapy is gonadotropin-releasing hormone (GnRH) agonists or antagonists [19].

GnRH Agonist

GnRH agonist may be the most effective drug in the management of myomas. It is an analogue of endogenus GnRH and binds to pituitary GnRH receptors (GnRH-R), leading to synthesis and release of the luteinizing hormone and follicular stimulating hormone. Compared with GnRH, GnRH agonist has a longer half-life that causes a continuous exposure of GnRH-R under the activity of GnRH agonists. Downregulation of GnRH-R consequently results in a decreased level of gonadotropin and suppressed production of the ovarian hormone [23–25]. GnRH agonists produce a transient menopausal condition.

The effects of GnRH agonists include decrements in the volume of myoma nodules and the uterus [25]. The decrease in myoma volume is variable, ranging from 27% to 70% [26–28]. Although GnRH agonist contributes to the shrinkage of myoma volume by inducing a transient menopausal status thereby resulting in low estrogen and low progesterone subsequently, the underlying mechanism of GnRH agonists in shrinking myomas is still controversial [29–31]. Many associated factors have been reported, including cellular atrophy, a decrease in cell proliferation, and reduced trophic mediators or uterine blood flow. Cellular atrophy of individual myoma cells may be due to a decrease in myofilaments within the myoma cells [32]. Changes in the number of myoma cells could be explained by increased cell necrosis and apoptosis [33–35], enhanced deoxyribonucleic acid damage and repair [36] or, possibly, vasoconstriction [37]. Since GnRH agonist can result in the menopausal status, menorrhagia can be alleviated [38] and myoma-related anemia be successfully treated by GnRH agonists [37].

There are various forms of GnRH agonists that may be administered intramuscularly, subcutaneously or by intranasal absorption [39]. These include leuprolide, buserelin, nafarelin, histrelin, goserelin, deslorelin, and triptorelin. The therapeutic effect is achieved by a reduction of median estradiol levels within an 80 to 180 pmol/L window [25]. In relation to alleviating menorrhagia, bleeding problems or related anemia are controlled in women after the first month of treatment. By reducing the uterine and myoma size, pain and pressure symptoms are relieved in the first 2 months. Maximal diminution of uterine and myoma size is achieved within the first 12 weeks of therapy [40]. However, the effect of GnRH agonists on the reduction of myoma size is transient. The reversal of estrogen deprivation takes about 4 weeks after discontinuation of GnRH agonist [41]. Most myoma nodules return to their initial size within about 6 months after discontinuation of GnRH agonist treatment. The rate of enlargement is rapid compared with natural enlargement [42], and regrowth of the uterus and myomas leads to a return of initial symptoms.

The significant disadvantages of GnRH agonists are hypoestrogenism-related untoward effects, resembling postmenopausal climacteric disturbances and bone loss [43,44]. Partial restoration of the estrogenic state by reduced-dose therapy or steroid "add-back" is proven to be effective for the relief of annoying side effects without the loss of the beneficial effects on myoma size and cycle suppression [45]. Addition of oral veralipride, a benzamide derivative, can reduce the vasomotor symptoms induced by a GnRH agonist [46]. Raloxifene or tibolone may also be the ideal add-back therapy to prevent bone loss but preserve the efficacy of GnRH agonists [47,48]. However, raloxifene

administration did not reduce vasomotor symptoms related to GnRH agonists [47]. In contrast, a significant reduction of hot flushes was observed when adding tibolone to GnRH agonist treatment [48,49]. Since GnRH agonists are expensive, several surveys have tried to investigate clinical parameters to predict the response to GnRH agonists. GnRH agonists have remarkable therapeutic efficacy in myomas, with the characteristics of a high concentration of unbound progesterone receptors [50], positive blood flow by Doppler ultrasound [51] but not in myomas with a hypoechoic appearance [52], high hyaline change or collagenous tissues [53], chromosomal rearrangement [54], or a pedunculated or cervical type [55]. In the management of myomas, GnRH agonists are currently assumed as an adjuvant therapy for preoperative preparation. The reduction of the myoma or uterine volume provides an advantage in simplifying the surgical procedure and decreasing operative morbidity (such as blood loss and operating time).

GnRH Antagonist

GnRH antagonists were concomitantly developed with GnRH agonists. However, the clinical application of GnRH antagonists is restricted by patient hypersensitivity. In contrast with the desensitization of GnRH-R by GnRH agonists, GnRH antagonists directly compete with endogenous GnRH for pituitary binding sites. GnRH antagonists suppress gonadotropin release within 4 to 8 hours in the absence of an initial "flare-up" effect. Theoretically, GnRH antagonists can achieve treatment effects similar to GnRH agonists within a shorter time span. However, the activity of GnRH antagonists is dose-dependent, and inhibitory effects should be attained by dose modification. Currently, GnRH antagonists are market-licensed for the indication of premature luteinizing hormone surge prevention in controlled ovarian hyperstimulation and the palliative treatment of advanced prostate cancer. The three commercially available GnRH antagonists are cetrorelix (Cetrotide; Serono International SA, Geneva, Switzerland), ganirelix (Orgalutran/Antagon; Organon, Oss, The Netherlands), and abarelix (Plenaxis; Praecis Pharmaceuticals Inc., Waltham, MA, USA).

Results of available clinical trials employing GnRH antagonists for the treatment of uterine myomas are indeterminate owing to uncontrolled settings, differences in regimen characteristics, and varied administration routes and dose sizes. Overall, ovarian suppression is observed within 48 hours, and a nadir of estradiol level is reached on day 7 of treatment [56,57]. Although shrinkage of uterine myomas by 25% to 50% may be observed after 2 to 8 weeks, a lack of response was frequently reported [58,59]. Variance in size reduction between individual patients makes the response to GnRH antagonists less reliable than predicted by the established usage of GnRH agonists.

Recently, cetrorelix acetate (Cetrotide; ASTA Medica AG, Halle, Germany), a more effective, longer acting, safer third-generation GnRH antagonist, showed increased apoptosis of leiomyoma cells in an *in vitro* study. The induced apoptosis may be associated with a deficiency of sex hormones as well as upregulation of pro-apoptotic factors expression [60]. The effect of GnRH agonists is temporary, as uterine myomas achieve their original size soon after treatment discontinuation. Therefore, the role of GnRH antagonists in the treatment of uterine myomas should be reserved as a feasible preoperative regimen.

Progesterone-mediated Intrauterine System

Levonorgestrel-releasing intrauterine system (LNg-IUS) is a T-shaped intrauterine device sheathed with a reservoir of 52 mg of 19-norprogestin levonorgestrel released at the daily rate of 20 μg [61]. Through its slow delivery of progesterone, LNg-IUS has been proven to reduce the duration of bleeding and the amount of menstrual loss owing to the inhibition of endometrial proliferation, as well as enhancement of cellular apoptosis [62]. It may be a therapeutic modality for myoma-associated menorrhagia and anemia [63,64]. The effect on reduction of myoma-related menorrhagia is weakened by an enlarged uterine cavity, severe blood loss prior to treatment, or irregular intermenstrual bleeding [65]. In terms of the reduction of uterine and myoma volume, an inconsistent effect was found during LNg-IUS use, and no significant differences were found in myoma volume after a 12-month usage of LNg-IUS [63].

Limitation of Medical Treatment

Without doubt, malignant uterine tumor should be an absolute contraindication of medical therapy [66]. Before we treat uterine myomas without evidence of pathology, the most important issue is to determine whether the uterine sarcomas arise from malignant transformation of pre-existing myomas [67,68]. If a physician is unable to answer this question with certainty, medical treatment for uterine myomas might carry a risk. For this reason, the pathogenesis of leiomyosarcoma and leiomyoma should be affirmed.

Conclusion

If no symptoms of uterine myomas exist, no therapy is required. Regular follow-up may be the first choice for women with uterine myomas. However, if symptoms or signs exist, treatment should be initiated without hesitancy. Most current medical therapy for uterine myomas is based on the hypothesis that uterine myoma is an ovarian steroid-dependent disease. Therefore, estrogen deprivation or progesterone-mediated therapy is always the choice if conservative or medical treatment is requested. Since estrogen deprivation in these relatively young women results in many unwanted side effects, combinations of several treatments for myomas may be a potential therapeutic modality in the future. The idea originated from an incidental finding of "add-back" therapy. Adjuvant therapy for relief of untoward effects is found to have additive benefit. Finally, with the advanced techniques of molecular biology, discovery of other myoma-related growth factors or the exploration of growth factor inhibitors in myomas will be an alternative in treating myomas. Besides medical treatment, other modalities, such as uterine artery embolization, ablative techniques and focused ultrasound surgery, may be alternative conservation treatment. Of course, definitive surgical treatment should not be neglected as a rescue method in the management of uterine myomas.

Acknowledgments

This work was supported, in part, by grants from Taipei Veterans General Hospital (V96C1-037, 96VN-008) and the National Science Council (NSC 96-2314-B-010-018-MY3), Taiwan.

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