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REVIEW ARTICLE

Medical Management of Uterine Leiomyoma: A Comprehensive Review

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ABSTRACT

Uterine leiomyomas are most common benign tumors that occur in women of reproductive age. They are frequently associated with symptoms that impact on quality of life and require treatment. Treatment was usually surgical with either hysterectomy or myomectomy being performed. Although myomectomy conserves the uterus, it is associated with complications that might not enhance the chance of pregnancy and for those concerned about fertility, alternatives are being developed. Apart from therapeutic modalities like uterine artery embolization, other exciting developments are high intensity focused ultrasound and MRI guided focused ultrasound. New medical treatments are being evaluated—among which the progesterone receptor modulators that induce amenorrhea and a degree of fibroid shrinkage whilst having minimal effect on ovarian function are promising. This article gives a comprehensive overview of medical management of leiomyoma, reviews the literature and suggests further reading.

Keywords: GnRH agonists for fibroids, Medical management, Ulipristal.

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INTRODUCTION

Uterine leiomyomas, or fibroids, are benign, hormone-sensitive, smooth-muscle tumors that occur in 20 to 40% of women of reproductive age.[1,2] The most common symptoms are abnormal uterine bleeding as menorrhagia, inter menstrual bleeding depending on site of myoma. Pelvic pain, dysmenorrhea, and pressure effects, which may adversely affect quality of life and fertility are other symptoms. Iron-deficiency anemia is also a common manifestation.[3-7] Majority require some intervention, and the choice of treatment is guided by the patient's age and desire to preserve fertility and avoid hysterectomy.[8] Fibroids are the most common indication for hysterectomy. Other treatments include myomectomy, hysteroscopic removal, uterine artery embolization, and various other interventions performed under radiologic guidance.[7,8]

Medical therapy is an option for women with symptomatic myomas who prefer nonsurgical treatment, and consider fertility preservation, or expect a less aggressive operation after shrinkage of the uterine volume.[9,10]

It has been well documented that fibroid growth and maintenance are stimulated by estrogen and are affected by cyclic hormonal changes. Estradiol and progesterone receptors have been identified in myomatous tissue and this fact may help in therapeutic hormonal manipulation of fibroids.[11] Receptor concentrations found to be varied with the menstrual cycle. The proliferative and mitotic counts were higher in the secretory phase and mitotic activity was significantly higher with progestin therapy. Aromatase P450, an estrogen synthase which has been identified within myomas may enable myomas to synthesize their own estrogen and promote myoma cell growth.[12]

Maruo et al[13] suggested progesterone has a dual effect on myomas. Progesterone stimulates leiomyoma cell growth by up regulating epidermal growth factor (EGF) and Bcl-2 Protein while down regulating tumor necrosis factor, inhibits myoma cell growth by down regulating insulin-like growth factor-1 (IGF-1) expression.

Local growth factors are involved in myoma growth and may mediate effects of estrogen and progesterone.

In this paper we will discuss the various available therapies for the medical management of myomas and review the current status of the medical management and discuss their risks and benefits.

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ESTROGEN AND PROGESTIN THERAPY

Combined hormonal contraceptives and progestational agents are commonly prescribed to regulate abnormal uterine bleeding, but appear to have limited efficacy in the treatment of uterine leiomyomas.[14,15] These drugs can be useful in some women with heavy menstrual bleeding, particularly those with coexisting problems (e.g. dysmenorrhea or oligoovulation); but they do not appear to be effective in decreasing bulk symptoms. There is also evidence that, in some women, contraceptive steroids may be associated with a decreased risk of uterine fibroids. There is one study that suggests that oral contraceptives started before age 16 may be associated with an increased risk of fibroids.[16]

Few studies have investigated the effects of oral contraceptive pills or progestins alone on myoma growth. Most studies have evaluated these medications in conjunction with Gonadotropin-releasing hormone (GnRH) analog. One study compared the low dose monophasic oral contraceptive with no treatment in 82 women with symptomatic myomas. Oral contraceptives were associated with a significantly decreased mean duration of menstrual flow from 5.8 to 4.4 days and increased mean hematocrit from 35.8 to 37.8% and no significant difference in mean uterine size as noted by bimanual examination and ultrasound at 12 months. Another study used data from Nurses' Health Study II to investigate any association between oral contraceptive use and incidence of myomas. Only women who first used oral contraceptives at 13 to 16 years of age had a significantly elevated risk for developing myomas.

Regarding progestin, studies have shown mixed results. Several have documented a decrease in the size of a myomatous uterus during progesterone therapy apart from reducing the amount of bleeding, increase in the hematocrit. In contrast some studies showed a marked enlargement of myomas during progestin therapy. *In vitro*, data also shows increased mitotic activity is greater with progesterone therapy, whereas the mitotic activity with estrogen progestin therapy and in controls was the same, showing that estrogen plus progestin may have minimal effect on myoma growth whereas there is significant potential for myoma growth with progestin therapy.

Levonorgestrel-releasing intrauterine system (LNG-IUS) has been studied as a local treatment for menorrhagia and symptomatic myomas. A myomatous uterus with an enlarged or distorted uterine cavity or sub mucosal myoma amenable to hysteroscopic resection is a contraindication for LNG-IUS.[17] In comparison of LNG-IUS *vs* conservative surgery or hysterectomy for heavy menstrual bleeding at 1 year there was no statistically significant difference in satisfaction rates or quality of life, though adverse effects were significantly less likely with conservative surgery (OR 0.24, 95% CI 0.11 to 0.49).[18]

There are no randomized trials evaluating the use of LNG-IUS for the treatment of menorrhagia related to uterine leiomyomas. Observational studies and systematic reviews have shown a reduction in uterine volume and bleeding, and an increase in hematocrit after placement of this IUS.[19-22] The device is a proven, effective, reversible treatment for menorrhagia and is now approved by the US Food and Drug Administration (FDA) for this indication. Another advantage is that it provides contraception for women who do not desire pregnancy. Griegorieva et al studied 67 premenopausal women with myomas of 12 weeks or less with menorrhagia and who desired LNG-IUS for contraception and concluded that LNG-IUS is an effective treatment for menorrhagia due to uterine myomas for patients who desire conservative management and contraception.[19] The levonorgestrel-releasing intrauterine system improves health-related quality of life significantly at relatively low cost. It is the most effective medical treatment for menorrhagia and comparable to surgical interventions.[24] Results from Maruo et al revealed that LNG-IUS may have variable effects on uterine myomas depending on the balance of growth factors in the local environment.[13] Understanding the molecular events involved in the transformation of a normal myometrial cell into a neoplastic cell and the subsequent growth of these leiomyoma cells will be important in determining the pathogenesis of these tumors and providing new targets for treatment.[23]

Progestin implants, injections, and pills—as with OCs, it is difficult to ascertain the effectiveness of progestin-only contraceptive steroids for treatment of leiomyomas. As with the breast, progesterone is a growth factor for myomas and may even be more critical than estrogen. But progestin-only contraceptives also cause endometrial atrophy and thus, provide relief of menstrual bleeding-related symptoms. They can be considered for treatment of mild symptoms, especially for women who need contraception. There is also consistent evidence from cohort studies that these agents may be associated with a decreased risk of leiomyoma formation.[25,26]

Although several of these therapies achieve some level of success, further studies are necessary to evaluate the current and long-term effects of these therapies.[27]

GnRH Agonists

Gonadotropin-releasing hormone agonist may be the most effective drug in the medical management of myomas. It is an analog of endogenous GnRH and binds to pituitary GnRH receptors (GnRH-R), leading to synthesis

and release of the luteinizing hormone and follicular stimulating hormone. GnRH agonist has a longer half-life than GnRH which causes a continuous exposure of GnRH-R to the activity of GnRH agonists leading to downregulation of GnRH-R. This results in a decreased level of gonadotropin and inhibits production of theovarian hormone.[28-30] GnRH agonists produce a transient menopausal condition.

The GnRH agonists cause reduction in the volume of myomas and the uterus.[30] The decrease in myoma volume is variable, ranging from 27 to 70%.[31-33] 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, many associated cellular changes, like cellular atrophy, a decrease in cell proliferation, and reduced trophic mediators or uterine blood flow have been described. Changes in the number of myoma cells could be explained by increased cell necrosis and apoptosis,[34-36] enhanced deoxyribonucleic acid damage and repair[37] or, possibly, vasoconstriction.[38] Since GnRH agonist can result in the menopausal status, menorrhagia can be alleviated[39] and myoma-related anemia be successfully treated.

The various forms of GnRH agonists include leuprolide, buserelin, nafarelin, histrelin, goserelin, deslorelin and triptorelin. They may be administered intramuscularly, subcutaneously or by intranasal absorption. Menorrhagia and related anemia are controlled in women after the first month of treatment. The pain and pressure symptoms are relieved in the first 2 months. Maximal reduction 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 temporary. After discontinuation of GnRH agonist, it takes about 4 weeks for reversal of antiestrogen effects.[41] Most myomas regain their initial size within about 6 months after discontinuation of GnRH agonist treatment. The rate of enlargement is also rapid compared with natural enlargement,[42] and leads to a return of initial symptoms.

Lethaby and et al[30] performed a systematic review of 26 randomized, controlled trials that evaluated the use of GnRH in patients before hysterectomy and myomectomy. They concluded that the use of GnRH analog for 3 to 4 months prior to fibroid surgery reduces both uterine volume and fibroid size. They are beneficial in the correction of preoperative iron deficiency anemia and reduce intraoperative blood loss. A midline incision can be converted to transverse incision and an abdominal procedure can be converted to a vaginal procedure.

The therapeutic effect of GnRH agonists is found to be high in myomas with high concentration of unbound progesterone receptors,[43] and increased blood flow by Doppler ultrasound.[44] The effect of GnRH agonists is less pronounced in myomas with hypoechoic changes,[45] hyaline changes or in fibroids with collagenous tissue.[46] Pedunculated or cervical fibroids also respond poorly to GnRH analog.[47] In the management of myomas, GnRH agonists are currently assumed as an adjuvant therapy for preoperative preparation.

The significant disadvantages of GnRH agonists are due to hypoestrogenism-related effects, which cause postmenopausal hormonal deficiency symptoms and bone loss.[48,49] 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.[50] Oral veralipride, a benzamide derivative, can reduce the vasomotor symptoms induced by a GnRH agonist.[51] Raloxifene or tibolone may also be the ideal add back therapy to prevent bone loss while preserving the efficacy of GnRH agonists.[52,53] A significant reduction of hot flushes was observed with tibolone. However, raloxifene administration did not reduce vasomotor symptoms related to GnRH agonists.[52]

GnRH Antagonists

In contrast to GnRH agonists, the antagonists compete for the receptors with endogenous GnRH on pituitary sites. They suppress the GnRH release within 4 to 8 hours without flaring up. 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). The present indications for GnRH antagonists are to prevent premature LH surge in controlled ovarian hyperstimulation, in treatment of advanced prostate cancer. The suppression of ovarian hormones starts at about 48 hours and the estradiol level falls to a minimum at about 1 week after administration. The response to treatment is variable and shrinkage of myomas varies from 25 to 50% in about 2 to 8 weeks. GnRH antagonists appear to be less reliable than predicted by the established usage of GnRH agonists.

Aromatase Inhibitors

Directly inhibit ovarian estrogen synthesis and hence, produce a hypoestrogenic state. The serum estrogen levels decrease within 24 hours in contrast to the flare up followed by hypoestrogenic state observed with GnRH antagonists. Aromatase is an estrogen synthetase which is known to be expressed by myomas. Aromatase inhibitors can be a promising therapy for myomas especially if they can be adapted to act preferentially on

myomas and spare ovarian estrogen synthesis. Further research is necessary on this group of medication in reproductive age population.

SERMs

They are nonsteroidal agents that bind to estrogen receptor and modulate its effects. Depending on the target tissue they exhibit either agonist or antagonist effects. Tamoxifen was studied for its effects on myomas[54] which concluded that it had marginal benefits for treating symptomatic myomas with unacceptable side effects.

Another SERM raloxifene was studied in postmenopausal women with a dose of 60 mg/day along with a placebo for 12 months. Significant response with respect to uterine size and myoma size was observed with less effect on normal myometrium.[55] Premenopausal women required a higher dose for the same response.

A combination of raloxifene and GnRH agonists was studied by Palomba et al.[56]

A significantly greater response in terms of greater decrease in the size of myoma was observed with combination of raloxifene with GnRH Agonist when compared to GnRH agonists alone. A stable suppression of myoma and uterine size with no noticeable change in the bone mineral density and endometrial proliferation was observed in 18 months of study period. The main side effect was hot flushes.

PROGESTERONE RECEPTOR MODULATORS

Mifeprestone is a progesterone receptor modulator which acts as an antagonist. High concentrations of progesterone receptors are noted in myoma compared with surrounding uterus. Mifeprestone acts on these receptors and reduces the number, thereby producing amenorrhea and myoma suppression. It maintains a hormonal state similar to the early follicular phase, and affects the vascular supply of myomas.[57] The dose used was 12.5 mg to 50 mg/day. The most common side effect was vasomotor symptoms. Steinauer et al[57] reviewed six clinical trials of mifepristone treatment for symptomatic myomas. Though the studies were small, not placebo controlled or blinded and overall heterogenous, they consistently demonstrated that mifepristone significantly decreased mean myoma volume and uterine volume, symptomatic relief from all myoma symptoms and 91% rate of amenorrhea. Endometrial hyperplasia may limit the long term use of mifepristone.

Selective progesterone receptor modulators (SPRMs) like SERMs they exhibit either agonist or antagonist activity which is progesterone specific and target tissue dependent.

Asoprisnil a SPRM directly affects endometrium with no change in estrogen concentration and ovulation. The doses tried in trials range from 5 mg to 25 mg/day.[58] Data show that asoprisnil is capable of suppressing uterine bleeding, myoma growth without affecting ovarian steroid production. The exact mechanism of these effects has to be elucidated and further research is warranted of this novel therapy.

Ulipristal acetate is also a selective progesterone receptor modulator that acts on progesterone receptors in myometrial and endometrial tissue and inhibits ovulation without causing large effects on estradiol levels or anti-glucocorticoid activity.[58,59]

A randomized, parallel-group, double-blind, placebo-controlled, phase 3 trial at 38 academic research centers in 6 countries,[60] in which ulipristal 5 and 10 mg and placebo was administered randomly in 2:2:1 ratio in women with heavy menstrual bleeding anemia and myomas for 13 weeks and the efficacy in relieving symptoms, reducing myoma volume and adverse effects profile was studied.[61]

The results confirmed, treatment with ulipristal acetate (at a dose of 5 mg or 10 mg) for 13 weeks before planned surgery was effective in controlling bleeding, decreasing fibroid volume, and reducing discomfort in women with menorrhagia and anemia. Headache and pain, discomfort, or tenderness in the breasts were the most common adverse events in the ulipristal acetate groups. Treatment with ulipristal acetate reduced fibroid volume without suppressing estradiol levels, which were in the mid follicular range in the ulipristal acetate groups. In contrast, GnRH agonists substantially reduce estrogen levels, with associated risks of bone loss.[37] The endometrial proliferative changes also were found to be reversible after 6 months of follow-up.

Androgens

Two androgenic preparations danazol and gestrinone have been studied in the treatment of myomas. Danazol has androgenic, moderate progestogenic, anti progestogenic and antiestrogenic properties. Gestrinone a derivative of ethinyl-nortestesterone and has antiestrogenic and antiprogesterone. The effect on myomas continues even after discontinuation of androgenic agents. The androgenic adverse effects, like weight gain, edema hirsutism, altered libido and rarely hepatocellular damage, fluid retention and spontaneous pregnancy loss preclude their use.

FUTURE DIRECTIONS

Current medical therapies include systemic as well as local manipulation of ovarian steroid hormones both

estrogen and progesterone. An ideal medical therapy should not affect ovulation, implantation, and embryo development. It should have minimal systemic side effects. The future therapies may aim at transforming and targeting growth factors involved in angiogenesis or fibrosis.

REFERENCES

1. Whitfield CR. editor. Dewhurst's Textbook of Obstetrics and Gynaecology for Postgraduates. 4th ed. London: Black well, 1986:726-733.
2. Wallach EE. In: Thompson JD, Rock JA, editors. TeLinde's Operative Gynaecology. 7th ed. Philadelphia: Lippincott, 1992.
3. Buttram Jr VC, Reiter RC. Uterine leiomyomas: etiology, symptomatology, and management. Fertil Steril 1981;36: 433-445.
4. Vercellini P, Vendola N, Ragni G, et al. Abnormal uterine bleeding associated with iron-deficiency anaemia: etiology and role of hysteroscopy. J Reprod Med 1993;38:502-504.
5. Wilson EA, Yang F, Rees ED. Estradiol and progesterone binding in uterine leiomyomata and in normal uterine tissue. Obstet Gynecol 1980;55:20-24.
6. Tamaya T, Fujimoto J, Okada H. Comparison of cellular levels of steroid receptors in uterine leiomyomas and myometrium. Acta Gynaecol Scand 1985;64:307-309.
7. Vollenhoven BJ, Pearce P, Herington AC, Healy DL. Steroid receptor binding and messenger RNA expression in fibroids from untreated and gonadotrophin-releasing hormone agonist pretreated women. Clin Endocrinol 1994;40(4): 537-544.
8. Matta WHM, Shaw RW, Nye M. Long-term follow-up of patients with uterine fibroids after treatment with the LHRH agonist buserelin. Br J Obstet Gynaecol 1989;96:200-206.
9. West CP, Lumsden MA, Baird DT. Goserelin (Zoladex) in the treatment of fibroids. Br J Obstet Gynaecol 1992;99(Suppl 7): 27-30.
10. Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L. Ulipristal Acetate versus Placebo for fibroid treatment before surgery. N Engl J Med 2012 Feb 2;366(5):409-420.
11. Lethaby A, Vollenhoven B, Sowter M. Efficacy of pre-operative gonadotrophin hormone releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy: a systematic review. BJOG: Int J Obstet Gynaecol 2002;109:1097-1108.
12. Shozu M, Sumitami H, Segawa T, et al Inhibition of in situ expression of aromatase P450 in leiomyoma of uterus by leuprolein acetate. J Clin Endocrinol Metab 2001;86(11): 5405-5411.
13. Maruo T, Matsuo H, Shimomura Y, et al. Effects of progesterone on growth factor expression in human uterine leiomyoma Steroids 2003;68(10-13):817-824.
14. Friedman AJ, Barbieri RL, Doubilet PM, et al. A randomized, double-blind trial of a gonadotropin releasing-hormone agonist (leuprolide) with or without medroxyprogesterone acetate in the treatment of leiomyomata uteri. Fertil Steril 1988;49:404.
15. Carr BR, Marshburn PB, Weatherall PT, et al. An evaluation of the effect of gonadotropin-releasing hormone analogs and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double blind, placebo-controlled, crossover trial. J Clin Endocrinol Metab 1993;76:1217.
16. Marshall LM, Spiegelman D, Goldman MB, Manson JE, Colditz GA, Barbieri RL, Stampfer MJ, Hunter DJ Fertil Steril. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata 1998;70(3):432.
17. Stewart EA. Overview of treatment of uterine leiomyomas (fibroids). In: Barbieri RL, Falk SJ, editors. Available at: www.uptodate.com.
18. Marjoribanks J, Lethaby A. Surgery versus medical therapy for heavy menstrual bleeding. Farquhar Cochrane Database Syst Rev 2006 Apr 19;(2):CD003855.
19. Grigorieva V, Chen-Mok M, Tarasova M, Mikhailov A. Use of a levonorgestrel-releasing intrauterine system to treat bleeding related to uterine leiomyomas. Fertil Steril 2003; 79(5):1194.
20. Starczewski A, Iwanicki M. Intrauterine therapy with levonorgestrel releasing IUD of women with hypermenorrhea secondary to uterine fibroids]. Ginekol Pol 2000;71(9):1221.
21. Magalhães J, Aldrighi JM, de Lima GR. Uterine volume and menstrual patterns in users of the levonorgestrel-releasing intrauterine system with idiopathic menorrhagia or menorrhagia due to leiomyomas. Contraception 2007;75(3):193.
22. Zapata LB, Whiteman MK, Tepper NK, Jamieson DJ, Marchbanks PA, Curtis KM. Intrauterine device use among women with uterine fibroids: a systematic review. Contraception 10;82(1):41.
23. Stewart EA, Novak RA. New concepts in the treatment of uterine leiomyomas. Obstet Gynecol 1998;92:624-627.
24. Hurskainen R, Paavonen J. Levonoegestrel releasing intrauterine system in the treatment of heavy menstrual bleeding. Curr O Pin Obstet Gynecol 2004;16(6):487-490.
25. Venkatachalam S, Bagratee JS, Moodley JJ. Medical management of uterine fibroids with medroxyprogesterone acetate (Depo Provera): a pilot study. Obstet Gynaecol 2004;24(7):798.
26. Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, Adams-Campbell LL, Rosenberg L. Reproductive factors, hormonal contraception, and risk of uterine leiomyomata in African-American women: a prospective study. Am J Epidemiol 2004;159(2):113.
27. Rackow BW, Arici A. Options for medical treatment of myomas. Obstet Gynecol Clin N Am 2006;33:97-113.
28. Adamson GD. Treatment of uterine fibroids: current findings with gonadotropin-releasing hormone agonists. Am J Obstet Gynecol 1992;166:746-751.
29. Broekmans FJ, Hompes PGA, Heitbrink MA, Netelenbos CC, Roos JC, Falke TM, Schoemaker J. Two-step gonadotropin releasing hormone agonist treatment of uterine leiomyomas standard-dose therapy followed by reduced-dose therapy. Am J Obstet Gynecol 1996;175:1208-1216.
30. Lethaby A, Vollenhoven B, Sowter M. Efficacy of pre-operative gonadotrophin hormone releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy: a systematic review. BJOG 2002;109:1097-1108.
31. Rutgers JL, Spong CY, Sinow R, Heiner J. Leuprolide acetate treatment and myoma arterial size. Obstet Gynecol 1995;86:386-388.
32. Watanabe Y, Nakamura G, Matsuguchi H, Nozaki M, Sano M, Nakano H. Efficacy of a low-dose leuprolide acetate depot in the treatment of uterine leiomyoma in Japanese women. Fertil Steril 1992;58:66-71.

33. Chia CC, Huang SC, Chen SS, et al. Ultrasonographic evaluation of the change in uterine fibroids induced by treatment with a GnRH analog. Taiwan J Obstet Gynecol 2006;45:124-128.
34. Colgan TJ, Pendergast S, LeBlanc M. The histopathology of uterine leiomyomas following treatment with gonadotropin releasing hormone analogues. Hum Pathol 1993;24:1073-1077.
35. Mizutani T, Sugihara A, Nakamuro K, Terada N. Suppression of cell proliferation and induction of apoptosis in uterine leiomyoma by gonadotropin-releasing hormone agonist (leuprolide acetate). J Clin Endocrinol Metab 1998;83: 1253-1255.
36. Higashijima T, Kataoka A, Nishida T, Yakushiji M. Gonadotropin-releasing hormone agonist therapy induces apoptosis in uterine leiomyoma. Eur J Obstet Gynecol Reprod Biol 1996;68:169-173.
37. Huang SC, Chou CY, Lin YS, Tsai YC, Hsu KF, Liu CH, Huang KE. Enhanced deoxyribonucleic acid damage and repair but unchanged apoptosis in uterine leiomyomas treated with gonadotropin-releasing hormone agonist. Am J Obstet Gynecol 1997;177:417-424.
38. Stovall TG, Muneyyirci-Delale O, Summitt RL Jr, Scialli AR. GnRH agonist and iron versus placebo and iron in the anemic patient before surgery for leiomyomas: a randomized controlled trial. Leuprolide Acetate Study Group. Obstet Gynecol 1995;86:65-71.
39. Wang PH, Chao HT, Lee WL. Rationale of myomectomy for perimenopausal women. Maturitas 2007;58:406-407.
40. Friedman AJ, Daly M, Juneau-Norcross M, Rein MS. Predictors of uterine volume reduction in women with myomas treated with a gonadotropin-releasing hormone agonist. Fertil Steril 1992;58:413-415.
41. Van Leusden HA. Impact of different GnRH analogs in benign gynecological disorders related to their chemical structure, delivery systems and dose. Gynecol Endocrinol 1994;8:215-222.
42. Rein MS, Friedman AJ, Stuart JM, MacLaughlin DT. Fibroid and myometrial steroid receptors in women treated with gonadotropin-releasing hormone agonist leuprolideacetate. Fertil Steril 1990;53:1018-1023.
43. Wang PH, Lee WL, Chao HT, Shu LP, Kao HL, Wu CW, Yuan CC. Relationship between hormone receptor concentration and tumor shrinkage in uterine myoma after treatment with a GnRHa. Zhonghua Yi Xue Za Zhi (Taipei) 1999;62: 294-299.
44. Yoshioka N. Usefulness of Doppler ultrasound in predicting the effect of gonadotropin-releasing hormone agonist (GnRHa) on myoma uteri. Nippon Sanka Fujinka Gakkai Zasshi 1995;47:1255-1260.
45. Zullo F, Pellicano M, Di Carlo C, De Stefano R, Marconi D, Zudi E. Ultrasonography prediction of the efficacy of GnRH agonist therapy before laparoscopy myomectomy. J Am Assoc Gynecol Laparosc 1998;5:361-366.
46. Kawamura N, Ito F, Ichimura T, Shibata S, Umesaki N, Ogita S. Correlation between shrinkage of uterine leiomyoma treated with buserelin acetate and histopathologic findings of biopsy specimen before treatment. Fertil Steril 1997;68:632-636.
47. Furui T, Imai A, Takagi A, Tamaya T, Takagi H, Matsunami K, Shiraki S. Differential efficacy of gonadotropin-releasing hormone (GnRH) agonist treatment on pedunculated and degenerated myomas: a retrospective study of 630 women. J Obstet Gynaecol 2000;20:504-506.
48. Wang PH, Horng HC, Cheng MH, Chao HT, Chao KC. Standard and low-dose hormone therapy for postmenopausal women—focus on the breast. Taiwan J Obstet Gynecol 2007; 46:127-134.
49. Wang PH, Cheng MH, Chao HT, Chao KC. Effects of tibolone on the breast of postmenopausal women. Taiwan J Obstet Gynecol 2007;50:121-126.
50. Maheux R, Lemay A, Blanchet P, Friede J, Pratt X. Maintained reduction of uterine leiomyoma following addition of hormonal replacement therapy to a monthly luteinizing hormone releasing hormone agonist implant: a pilot study. Hum Reprod 1991;6:500-505.
51. Vercellini P, Sacerdote P, Trespidi L, Manfredi B, Panerai AE, Crosignani PG. Veralipride for hot flushes induced by a gonadotropin-releasing hormone agonist: a controlled study. Fertil Steril 1994;62:938-942.
52. Palomba S, Orio F Jr, Russo T, et al. Long-term effectiveness and safety of GnRH agonist plus raloxifene administration in women with uterine leiomyomas. Hum Reprod 2004;19: 1308-1313.
53. Palomba S, Affinito P, Di Carlo C, Bifulco G, Nappi C. Long term administration of tibolone plus gonadotropin-releasing hormone agonist for the treatment of uterine leiomyomas: effectiveness and effects on vasomotor symptoms, bone mass and lipid profiles. Fertil Steril 1999;72:889-895.
54. Sadan O, Ginath S, Sofer D, et al. The role of tamoxifen in the treatment of symptomatic uterine leiomyomata: a pilot study. Eur J Obstet Gynecol Reprod Biol 2001;96(2):183-186.
55. Palomba S, Orio Jr F, Moreli M, et al. Raloxifene administration in premenopausall women with uterine leiomyomas in postmenopausal women. Fertil Steril 2001;76(1):38-43.
56. Palombo S. Russo T Orio Jr. Fetal Effectiveness of combined GnRH analogue plus raloxifene administration in the treatment of uterine leiomyomas : a prospective, randomized, single blind placebo controlled clinical trial Hum Reprod 2002;17(12):3213-3219.
57. Steinauer J, Pritts EA, Jackson R, et al. Systematic review of mifeprestone for the treatment of uterine leiomyomata Obstet Gynecol 2004;103(6):1331-1336.
58. Chwalisz K, Parker RL, Williamsons S, et al. Treatment of uterine leiomyomas with the novel SPRM J. Soc Gynecolol Investig 2003;10(2 suppl): Abstract 301A.
59. Chabbert-Buffet N, Pintiaux-Kairis A, Bouchard P. Effects of the progesterone receptor modulator VA2914 in a continuous low dose on the hypothalamic-pituitary ovarian axis and endometrium in normal women: a prospective, randomized, placebo-controlled trial. J Clin Endocrinol Metab 2007;92:3582-3589.
60. Attardi BJ, Burgenson J, Hild SA, Reel JR, Blye RP. CDB-4124 and its putative monodemethylated metabolite, CDB-4453, are potent antiprogestins with reduced anti glucocorticoid activity: in vitro comparison to mifepristone and CDB-2914 Mol Cell Endocrinol 2002;188:111-123.
61. Donnez J, Bouchard P. Ulipristal Acetate versus placebo for fibroid treatment before surgery. N Engl J Med 2012 Feb 2;366-365.