Gynecol Surg (2005) 2: 7–13
DOI 10.1007/s10397-004-0078-0

REVIEW ARTICLE

Stefano Palomba · Angela Falbo · Tiziana Russo
Fulvio Zullo

GnRH analogs for the treatment of symptomatic uterine leiomyomas

Received: 12 July 2004 / Accepted: 16 December 2004 / Published online: 18 February 2005

Abstract Uterine leiomyomas are the most frequent benign disease of the female reproductive tract. To date, the standard treatment of uterine leiomyomas is laparotomic/laparoscopic excision in women who want to preserve their fertility, whereas the use of a more extensive surgery, such as hysterectomy, is reserved for disseminated uterine leiomyomatosis, usually in the perimenopausal period. Given the pathogenesis of uterine leiomyomas, it is clear that future treatments for leiomyomas may be medical. At present the only clinically relevant medical treatment of uterine leiomyoma is GnRH agonist administration in depot formulations. In this review, the use of GnRH agonists, with or without "add-back therapy," and antagonists will be assessed.

Keywords GnRH agonist · GnRH antagonist · GnRH analog · Add-back therapy · Uterine leiomyomas

Introduction

Uterine leiomyomas are the most frequent benign disease of the female reproductive tract. They are found in at least 20–25% of fertile women and in 50% of women studied postmortem [1]. Between 20% and 50% of cases of uterine leiomyomas cause clinical symptoms (menorrhagia, infertility, recurrent abortion, pelvic pain, and so on) requiring treatment [1]. Thus, this disease is one of the main causes of health expenditure in the field of gynecology [1]. In fact, symptomatic uterine leiomyomatosis is the surgical indication for about two-thirds of hysterectomies, and this statistic is even more relevant because hysterectomy is the most frequent major surgery in women [1].

However, the pathogenesis of uterine leiomyomas is still not well defined. Uterine leiomyomas have been demonstrated to be estrogen-dependent monoclonal tumors [2–4]. The primum movens is probably a genetic mutation and thus an alteration of the intratumoral estrogenic metabolism [5–8]. The transcription and the expressivity of the estrogen receptor, in fact, is increased in the myoma tissue when compared with healthy myometrium [6, 7]. A specific distribution of estrogen receptor subtypes has been demonstrated. Specifically, it seems that, despite high concentrations of mRNA for estrogen receptor alpha, there is not a relationship in concentrations in the same receptor. On the contrary, concentrations of the beta receptors twofold to threefold higher in comparison with normal myometrium have been detected [8]. The simple action of estrogens does not seem to be the only pathogenic cause. Progesterone could play a pivotal role in transforming normal myometrial cell to myomatous cells [9, 10]. High progesterone levels, such as those detected in the luteal phase of the menstrual cycle, or after medroxyprogesterone acetate (MPA) administration are related to an increase in mitotic activity of the myoma cells [11, 12]. Finally, in the myomatous tissue, similarly to the estrogen receptors, there is overexpression of progesterone receptors [3].

To date, the standard treatment for uterine leiomyomas is laparotomic/laparoscopic excision in women who want to preserve their fertility. The use of more extensive surgery is reserved for disseminated uterine leiomyomatosis, especially in the perimenopausal period. Given the pathogenesis of uterine leiomyomas (see below), it is clear that future treatment of leiomyomas will be essentially medical.

S. Palomba · A. Falbo · T. Russo · F. Zullo
Department of Obstetrics and Gynecology, University Magna Graecia of Catanzaro, Catanzaro, Italy

S. Palomba (✉)
Via E. Nicolardi 188, Naples, 80131, Italy
E-mail: stefanopalomba@tin.it
Tel.: +39-81-7434194
Fax: +39-961-728329

Medical treatments

Several medical therapies have been proposed for treating uterine leiomyomas (Table 1). In clinical practice it is very common to administer oral contraceptives to patients affected by uterine leiomyomas [13–15]. The rationale for their administration includes regulating menstrual bleeding and decreasing the length of bleeding and the severity of menorrhagia [13]. Some studies [14, 15] have defined oral contraceptive administration as a causal factor in tumoral growth. In these cases, oral contraceptives should be stopped [14, 15].

The use of mifepristone (RU486), a drug with weak antiprogestin actions, in a dosage of 10 mg/day induces the reduction of progesterone receptors and leiomyoma dimensions [16, 17]. Gestrinone at doses of 2.5 mg or 5 mg two to three times per week has also been proposed for treating uterine leiomyomas [18–20]. Recent data confirm that danazol administration is also effective for treating patients with uterine leiomyomas [21]. In particular, it has been demonstrated that 400 mg daily of danazol for 4 months decreases leiomyomas by 25% with an action due to hypoestrogenism and antiprogestin [21]. However, in both of the latter therapeutic regimens, the treatment has several side effects, such as weight gain, seborrhea, acne, and hirsutism, that are related to an androgenic action of the drugs.

New hypotheses for treatment have been recently published in the literature [22–24]. The use of GnRH analogs (GnRH-a) seems to be a real and valid therapeutic option.

GnRH analogs (GnRH-a)

The GnRH-a is a group of drugs with an agonist/antagonist action on the GnRH receptor. Their effects are related to the action on the GnRH receptor of the pituitary gland.

GnRH agonists

GnRH agonists induce a profound downregulation of the pituitary with a subsequent postreceptor message blockage for gonadotropin synthesis and secretion. After a rapid secretion of gonadotropins (''flare-up'' effect) during the first 2 weeks of treatment, there is a weak inhibition of pituitary function with inhibition of follicular development, anovulation, and a reversible hypogonadotropic hypogonadism state [24–25].

The first agonist used in the conservative treatment of uterine leiomyomas was reported by Filicori et al. [25] in 1983. Specifically, they showed the effectiveness of GnRH agonist administration in women affected by symptomatic uterine leiomyomas.

The use of GnRH agonists induces a significant reduction in leiomyoma size within only 8–10 weeks, achieving the highest reduction after 14 weeks of treatment. After this period, the volume reduction achieves a steady state. After treatment withdrawn, estrogen levels return to the normal range within about 1 month, and leiomyoma size returns to pretreatment dimensions after about 3 months [26–29]. The disease will cause symptoms again due to the leiomyoma's regrowth.

The efficacy of these drugs, after careful patient selection, is about 90%, and they are a valid alternative to surgical intervention.

GnRH agonists have wide variability in terms of clinical efficacy. For this reason it is necessary to study the possible clinical response to treatment before drug administration [30–34]. In 1992 Hackenberg et al. [33] showed that after only 1 month of treatment, it is possible to define the patient as a ''poor responder.'' In these cases the risk-benefit ratio cannot be considered acceptable. Our data [31, 32] demonstrated that an ultrasound assessment of the echographic pattern of leiomyomas is important to decide whether to treat or not. GnRH analogs seem to have a reduced efficacy in the presence of hypo- or hyperechoic leiomyomas [31, 32]. Also, the use of magnetic resonance imaging has shown its efficacy in detecting leiomyomas more or less susceptible to medical treatment [35].

Another important factor that probably plays a role in the effectiveness of GnRH agonists is patients' age. In particular, efficacy is higher in women under 35 years than in older women. Leiomyoma volume did not influence the response to treatment, but the evaluation of leiomyoma size is an important tool in predicting the

Table 1 Medical therapies for uterine leiomyomas

Treatment	Efficacy	Side effects	Main administration route	Duration of therapy	Cost
Progestins	No	Possible increase in tumor size	Oral	Long-term	Low
Oral contraceptives	Poor	Possible increase in tumor size	Oral	Long-term	Low
Danazol	Good	Weight gain, mild hyperandrogenism	Oral	Long-term	Not expensive
Gestrinone	Good	Weight gain, mild hyperandrogenism	Oral	Long-term	Low
Mifepristone	Good	Mild hot flashes	Oral	Long-term	Low
GnRH agonists	Very good	Climacteric-like symptoms, metabolic syndrome, bone loss	Intramuscular	Short-term	Very expensive
GnRH agonist plus add-back therapy	Very good	Very long-term data unknown	Intramuscular and oral	Long-term	Very expensive
GnRH antagonists	Unknown	Unknown	Intramuscular	Shot-term	Very expensive
Raloxifene	No	Leg cramps	Oral	No data	Expensive

efficacy of GnRH agonists. In fact, the presence of histological (fat and calcific) degeneration and high vascularity in large leiomyomas is related to a lowered response to conservative therapy.

The significant decrease of uterine and leiomyoma volumes induced by GnRH agonist treatment [36] should be due to a relative vasoconstriction of myomatous vessels [37, 38] and/or to diminished nitric oxide production [39]. In fact, the average diameter of intramyomatous arteries was 24% smaller in patients treated with GnRH-a compared with those receiving placebo [38]. In addition, arteriosclerotic changes, including intimal and medial fibrosis, were seen more often in the subjects treated with GnRH agonists [38]. Finally, GnRH-a act directly on myomatous cells by specific GnRH receptors, inducing a suppression of cell proliferation and promoting the apoptosis [37, 40].

There are several protocols for analog administration [41]. GnRH-a are usually administered in the early follicular phase (day 2–3 of the menstrual cycle). They are used preoperatively for 2 or 3 months in short-term protocols both to reduce fibroid and uterine volume and to control bleeding, whereas long-term protocols (over 6 months) are used in perimenopausal women to induce an iatrogenic climacteric state in the long-term nonsurgical management of symptomatic leiomyomas [41]. This is one of the most important challenges of endocrinological gynecology.

In a recent systematic review [42] that included only randomized controlled trials, it was shown that GnRH agonist therapy prior to surgery significantly improves pre- and postoperative hemoglobin and hematocrit and reduces intraoperative blood loss. Hysterectomy appeared to be easier after pretreatment with GnRH analog therapy; operating time was reduced, and more hysterectomy patients were able to have vaginal rather than abdominal procedures. In addition, the presence of small myomas is not a limitation in the preoperative use of analogs [42].

A recent study [34] showed that intermittent courses of GnRH agonists could be used in the nonsurgical management of women with symptomatic leiomyomata uteri. Specifically, each month of GnRH agonist therapy produced an average of 3 months of symptom control; in other words, a 6-month course of a GnRH agonist could be expected on average to produce 18 months of symptom control.

Nevertheless these results were obtained for treatments of at least of 6 months and there is no evidence demonstrating beneficial effects after stopping treatment with shorter courses of agonists.

To date, it seems that the use of intermittent 6-month courses of GnRH agonists is effective in treating leiomyoma symptoms, avoiding the profound hypoestrogenic state, and limiting the climacteric-like symptoms. In fact, the response of the pituitary ovarian axis to GnRH agonists administration is highly subjective. It is possible that the same dose of analog is effective in some women and ineffective in others. For this reason, the dosage of GnRH agonist could be adjusted considering the clinical response in terms of estradiol levels and leiomyoma size.

Both short- and long-term treatments with GnRH agonists are associated with several side effects because of the profound hypoestrogenic state [43–45]. The hypoestrogenism induced by the use of GnRH agonists causes several climacteric-like symptoms such as hot flashes, vaginal dryness, reduced libido, metabolic alterations, cognitive deficits, and, above all, bone loss that varies from 0.8% to 7% after 12 months of GnRH agonist administration [41, 43–46]. Notwithstanding the metabolic alterations recently studied in women treated with GnRH agonists [47], at the present there is no clear evidence of cardiovascular risk related to GnRH agonist treatment [41, 43–46].

For GnRH agonist administration beyond 6 months, it has been postulated that the addition of low doses of steroids (“add-back therapy”) may avoid the adverse effects due to the prolonged hypoestrogenism state without reducing the efficacy of analog alone [41, 43–46].

Add-back therapy

Friedman et al. [45] described a pilot study in women with uterine leiomyomas treated with GnRH agonists [46]. They added small amounts of estrogen to increase circulating estrogens to levels high enough to maintain the integrity of some tissue with relief of vasomotor symptoms while causing other tissues to remain in a state of regression (“threshold hypothesis”) [45].

Several drugs have been proposed as add-back therapy in the treatment of uterine leiomyomas. The addition of progestins (MPA 20 mg/day) at the start of the GnRH agonist treatment induces a reduction in uterine volume compared with analog alone [48]. On the contrary, it seems to be more effective to start the treatment with the analog alone and to add the add-back therapy only after 3 months [41]. After this “window period” of 3 months, the estro-progestin addition (0.75 mg estropipate daily plus 0.7 mg norethisterone acetate [NETA] sequentially added) is more effective than only progestin coadministration (NETA, 10 mg/day) in terms of leiomyoma size reduction [43, 44]. Furthermore, the adverse effects of GnRH agonists were reduced in both add-back therapy regimens, with no difference between them. After a follow-up of 6 months, both add-back therapy regimens were similarly effective in reducing leiomyoma size. No difference in estro-progestin administration has been shown between continuous or cyclic regimens [41].

A recent study [49] carried out on a small number of subjects demonstrated that estradiol administration after 2 months of GnRH analog treatment alone is effective in reducing bone loss and vasomotor symptoms without compromising the efficacy of treatment with an analog alone.

Tibolone seems to be an ideal drug with steroid activity that may be administered in association with GnRH-a as add-back therapy. Tibolone is a synthetic compound structurally related to norethynodrel, with weak estrogenic, androgenic, and progestogenic properties. It has been successfully used to treat women with climacteric complaints and to prevent bone loss in postmenopausal women [50] without significant endometrium stimulation [51]. Several studies have demonstrated the efficacy of tibolone in association with GnRH-a in treating postmenopausal women with uterine leiomyomas [52–54].

Palomba et al. [55] have demonstrated in a randomized double-blind placebo-controlled study that GnRH agonists alone or a GnRH agonist plus tibolone administration at the standard dose of 2.5 mg/day is similarly effective in terms of reducing uterine leiomyoma volume and myoma-related symptoms. In addition, tibolone reduced the mean number of hot flashes per day and prevented bone loss due to agonist treatment [55–57].

After 2 years of observation, a lower mean number of hot flashes per day was observed when compared with placebo [57]. Women treated with tibolone showed bone metabolism and an incidence of vaginal bleeding similar to those of women treated with analog alone; the reduction of uterine and leiomyoma volume remained constant throughout the study period [57]. After 6 months of follow-up, when the GnRH agonist was stopped, some perimenopausal women began menstruating, and an increase in leiomyoma size similar to that in the pretreatment phase was observed.

Tibolone is effective not only in long-term protocols [56, 57] but also in short-term ones [55]. In particular, after 2 months of presurgical treatment, GnRH agonist plus tibolone administration significantly reduced the duration of laparoscopic myomectomy and intraoperative bleeding, as did GnRH agonist plus placebo administration [55].

A recent study by Somekawa [58] evaluated the efficacy of the addition of ipriflavone in women with uterine leiomyomas treated with a GnRH agonist. Ipriflavone effectively alleviated the adverse effects of estrogen deficiency without reducing the efficacy of the GnRH agonist. Specifically, GnRH agonist plus ipriflavone administration reduced bone loss, with a reduction rate of 3.70% after 6 months of treatment.

Preclinical [59–63] and clinical [23] data have suggested that raloxifene may have a beneficial effect on leiomyomas. In fact, in a recent clinical study [23], a significant reduction in leiomyoma size after 1 year of treatment with 60 mg of raloxifene daily was observed in postmenopausal women. In contrast, the administration of raloxifene at standard and high doses to premenopausal women affected by uterine leiomyomas did not induce any reduction in uterine or leiomyoma sizes [64].

Based on these findings, we studied the efficacy of raloxifene as add-back therapy in women with uterine leiomyomas treated with GnRH analogs [65, 66]. In this last study, we compared in a randomized single-blind placebo-controlled fashion the administration of GnRH analog plus raloxifene versus GnRH analog alone. A significant decrease in uterine, leiomyoma, and not-leiomyoma sizes was detected in both treatment groups compared with baseline. Leiomyoma sizes were not significantly lower in the GnRH-analog-plus-raloxifene group than in the GnRH-analog-alone group, but no difference was observed in leiomyoma-related symptoms between the groups throughout the study period [65]. No significant variation in bone metabolism was detected during treatment with GnRH analog plus raloxifene [66].

In a subanalysis of the study [47], we observed that GnRH analog altered serum lipoproteins and homocysteine levels and increased insulin resistance. But when raloxifene was added to the GnRH analog, these acute metabolic changes were prevented or reduced [47]. However, raloxifene did not reduce the cognitive deficits observed during GnRH analog administration [67].

Finally, GnRH analog plus raloxifene is a safe pharmacological association in long-term studies [68] and improves the patient's mood and quality of life [67].

During our study period few side effects were detected, and raloxifene treatment was tolerated as well as placebo. Raloxifene administration did not reduce the vasomotor symptoms related to GnRH-analog. In contrast, a significant reduction in the mean number of hot flashes per day was observed when tibolone was added to GnRH-a treatment [55–57, 69].

Raloxifene and tibolone are two compounds that did not induce endometrial proliferation in postmenopausal women with a high percentage of ''not bleeding'' cycles [70]. Our data confirm these findings. In fact, the addition of tibolone [56] or raloxifene to GnRH-a treatment in women with uterine leiomyomas did not increase the percentage of women with uterine bleeding compared with analog alone.

GnRH antagonists

The GnRH antagonists bind to gonadotrope GnRH receptors and compete successfully with endogenous agonist GnRH molecules for receptor occupancy [71]. Within a few hours, GnRH antagonists link competitively with GnRH receptors with no activation or stimulation of these receptors. Thus, no flare-up effect is observed when the agonist is administered. Specifically, the GnRH antagonist desensitization of gonadotropes induces an immediate decrease in the concentration of gonadotropins and a subsequent reduction in estradiol levels [71].

Hypoestrogenism induced by GnRH antagonists rapidly leads to improvement in uterine bleeding and shrinkage in myoma dimensions [72, 73], particularly in submucosal ones [73]. In fact, the maximum reduction is achieved within 2 weeks of treatment, a shorter time in comparison with GnRH agonist use.

These advantages have a clinical relevance in the preoperative treatment of uterine leiomyomas [74].

The local tolerance of GnRH antagonists is generally good, but the percentage of patients with moderate or severe local tolerance reaction is higher than with GnRH analog. [71].

In a randomized study, Felberbaum et al. [73] evaluated the effectiveness of a depot preparation of third-generation GnRH antagonist for preoperative treatment in premenopausal women with symptomatic uterine leiomyomas who were undergoing surgery. A mean leiomyoma volume shrinkage rate of 31.3% after 14 days of treatment was observed. More recently, Hara et al. [75] have experimented with a nonpeptide orally active GnRH antagonist in an animal model, suggesting its use also for reproductive disorders.

Conclusions

At the moment, the only medical treatment for uterine leiomyomas is GnRH agonist administration in depot formulations. To reduce the GnRH agonist side effects, we recommend the coadministration of raloxifene at the start of treatment to maximize the efficacy in reducing uterine and leiomyoma size.

Future studies should evaluate the efficacy and safety of new depot formulations of GnRH antagonists in reducing the size and the symptoms of leiomyomas.

References

1. Steward EA (2001) Uterine fibroids. Lancet 357:293–298
2. Chegini N, Rong H, Dou Q, Kipersztok S, Williams RS (1996) Gonadotropin-releasing hormone (GnRH) and GnRH receptor gene expression in human myometrium and leiomyomata and the direct action of GnRH analogs on myometrial smooth muscle cells and interaction with ovarian steroids in vitro. J Clin Endocrinol Metab 81:3215–3221
3. Englund K, Blanck A, Gustavsson I, Lundkvist U, Sjoblom P (1998) Sex steroids receptors in human myometrium and fibroids: changes during the menstrual cycle and gonadotropin-releasing hormone treatment. J Clin Endocrinol Metab 83:92–96
4. Higashijima T, Kataoka A, Nishida T, Yakushiji M (1996) Gonadotropin-releasing hormone agonist therapy induces apoptosis in uterine leiomyoma. Eur J Obstet Gynecol Reprod Biol 68:169–173
5. Pasqualini JR, Cornier E, Grenier J, Vella C, Schatz B, Netter A (1990) Effect of decapeptyl, an agonist analog of gonadotropin-releasing hormone on estrogens, estrogen sulfates, and progesterone receptors in leiomyomata and myometrium. Fertil Steril 53:1012–1017
6. Yamamoto T, Takamori K, Okada H (1984) Estrogen biosynthesis in leiomyomata and myometrium of the uterus. Horm Metab Res 16:678–679
7. Bulun SE, Simpson ER, Word RA (1994) Expression of the CYP19 gene and its product aromatase cytochrome P450 in human uterine leiomyoma tissue and cells in culture. J Clin Endocrinol Metab 78:736–743
8. Benassayag C, Leroy MJ, Rigourd V, Robert B, Honore JC, Mignot TM (1999) Estrogen receptors (ERalpha/ERbeta) in normal and pathological growth of the human myometrium: pregnancy and leiomyoma. Am J Physiol 276:1112–1118
9. Rein MS, Barbieri RL, Friedman AJ (1995) Progesterone: A critical role in pathogenesis of uterine myomas. Am J Obstet Gynecol 172:14–18
10. Tiltman AJ (1985) The effect of progestins on the mitotic activity of uterine fibromyomas. Int J Gynecol Pathol 4:89–96
11. Kawaguchi K, Fujii S, Konishi I, Nanbu Y, Nonogaki H, Mori T (1989) Mitotic activity in uterine leiomyomas during the menstrual cycle. Am J Obstet Gynecol 160:637–641
12. Rein MS (2000) Advanced in uterine leiomyoma research: the progesterone hypothesis. Environ Health Perspect 108:791–793
13. Friedman AJ, Thomas PP (1995) Does low-dose combination oral contraceptive use affect uterine size or menstrual flow in premenopausal with leiomyomas? Obstet Gynecol 85:631–635
14. Barbieri RL (1997) Reduction in the size of a uterine leiomyoma following discontinuation of an estrogen-progestin contraceptive. Gynecol Obstet Invest 43:276–277
15. Marshall LM, Spiegelman D, Goldman MB, Manson JE, Colditz G, Barbieri RL, Stampfer MJ, Hunter DJ (1998) A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. Fertil Steril 70:432–439
16. Murphy AA, Kettel LM, Morales AJ, Roberts VJ, Yen SSC (1993) Regression of uterine leiomyomata in response to the antiprogesterone RU 486. J Clin Endocrinol Metab 76:513–517
17. Kertel LM, Murphy AA, Morales AJ, Yen SS (1994) Clinical Efficacy of antiprogesterone RU 486 in the treatment of endometriosis and uterine fibroids. Hum Reprod 9:116–120
18. Coutinho EM, Goncalves MT (1989) Long-term treatment of leiomyomas with gestrinone. Fertil Steril 51:939–946
19. Coutinho EM (1989) Gestrinone in the treatment of myomas. Acta Obstet Gynecol Scand 150:39–46
20. Coutinho EM (1990) Treatment of large fibroids with high doses of getrinone. Gynecol Obstet Invest 30:44–47
21. De Leo V, La Marca A, Morgante G (1999) Short-term treatment of uterine fibromyomas with danazol. Gynecol Obstet Invest 47:258–262
22. De Leo V, La Marca A, Morgante G, Severi FM, Petraglia F (2001) Administration of somatostatin analogue reduces uterine and myoma volume in women with uterine leiomyomata. Obstet Gynecol 75:632–633
23. Palomba S, Sammartino A, Di Carlo C, Affinito P, Zullo F, Nappi C (2001) Effects of raloxifene treatment on uterine leiomyomas in postmenopausal women. Fertil Steril 76:38–43
24. Minakuchi K, Kawamura N, Tsujimura A (1999) Remarkable and persistent shrinkage of uterine leiomyoma associated with interferon alfa treatment for hepatitis. Lancet 353:2127–2128
25. Filicori M, Hall DA, Loughlin JS, Rivier J, Vale W, Crowley WF Jr (1983) A conservative approach to the management of uterine leiomyoma: pituitary desensibilization by a luteinizing hormone-releasing hormone analogue Am J Obstet Gynecol 147:726–727
26. Brosens TA (1997) Variable response of uterine leiomyomas after GnRH agonist therapy. Fertil Steril 68:948–949
27. Healy DL, Lawson SR, Abbott M, Baird DT, Fraser HM (1986) Toward removing uterine fibroids without surgery: subcutaneous infusion of a luteinizing hormone-releasing hormone agonist commencing in the luteal phase. J Clin Endocrinol Metab 63:619–625
28. Maheux R, Guilloteau C, Lemay A, Bastide A, Fazekas AT (1984) Regression of leiomyomata uteri following hypoestrogenism induced by repetitive luteinizing hormone-releasing hormone agonist treatment: preliminary report. Fertil Steril 42:644–646
29. Maheux R, Guilloteau C, Lemay A, Bastide A, Fazekas AT (1985) Luteinizing hormone-releasing hormone agonist and uterine leiomyoma: a study pilot. Am J Obstet Gynecol 152:1034–1038

30. Vollenhoven BJ, Shekleton P, McDonald J, Healy DL (1990) Clinical predictors for buserelin acetate treatment of uterine fibroids: a prospective study of 40 women. Fertil Steril 54:1031–1038
31. Palomba S, Zullo F (2001) Leuprolide: as needed? Fertil Steril 76:216–217
32. Zullo F, Pellicano M, Di Carlo C, De Stefano R, Marconi D, Zupi E (1998) Ultrasonographic predictor of the efficacy of GnRH agonist therapy before laparoscopic myomectomy. J Am Assoc Gynecol Laparosc 5:361–366
33. Hackenberg R, Genenhues T, Deiehert U, Duda V, Schmidt-Rhode P, Schulz KD (1992) The response of uterine fibroids to GnRH-agonist treatment can be predicted in most cases after one month. Eur J Obstet Gynecol Reprod Biol 45:125–129
34. Scialli AR, Levi AJ (2000) Intermittent leuprolide acetate for the nonsurgical management of women with leiomyomata uteri. Fertil Steril 74:540–546
35. Takahashi K, Okada M, Imaoka I, Sugimura K, Miyazaki K (2001) Value of magnetic resonance imaging in predicting efficacy of GnRH analogue treatment for uterine leiomyoma. Hum Reprod 16:1989–1994
36. Aleem FA, Predanic M (1995) The hemodynamic effect of GnRH agonist therapy on uterine leiomyoma vascularity: a prospective study using transvaginal color Doppler sonography. Gynecol Endocrinol 9:253–258
37. Yamamoto H, Sato H, Shibata S, Murata M, Fukuda J, Tanaka T (2001) Involvement of annexin V in the antiproliferative effect of GnRH agonist on cultured human uterine leiomyoma cells. Mol Hum Reprod 7:169–173
38. Rutgers JL, Spong CY, Sinow R, Heiner J (1995) Leuprolide acetate treatment and myoma arterial size. Obstet Gynecol 86:386–388
39. Gokdeniz R, Ozen S, Mizrak B, Bazoglu N (2000) GnRH agonist decreases endothelial nitric oxide synthetase (eNOS) expression in leiomyoma. Int J Obstet Gynecol 70:347–352
40. Mizutani T, Sugihara A, Nakamuro K, Terada N (1998) Suppression of cell proliferation and induction of apoptosis in uterine leiomyoma by gonadotropin-releasing hormone agonist (leuprolide acetate). J Clin Endocrinol Metab 83:1253–1255
41. Pickersgill A (1998) GnRH agonists and add-back therapy: is there a perfect combination ? Br J Obstet Gynaecol 105:475–485
42. Lethaby A, Vollenhoven B, Sowter M (2001) Pre-operative GnRH-analogue therapy before hysterectomy or myomectomy for uterine fibroids. (Cochrane review). In: The Cochrane library, issue 1, Update Software, Oxford
43. Friedman AJ, Daly M, Juneau-Norcross M, Rein MS, Fine C, Gleason R, Leboff M (1993) A prospective, randomized trial of gonadotropin-releasing hormone agonist plus estrogen-progestin or progestin "add-back" regimens for women with leiomyomata uteri. J Clin Endocrinol Metab 76:1439–1445
44. Friedman AJ, Daly M, Juneau-Norcross M, Gleason R, Rein MS, Leboff M (1994) Long-term medical therapy for leiomyomata uteri: a prospective, randomized study of leuprolide acetate depot plus either oestrogen-progestin or progestin "add-back" for 2 years. Hum Reprod 9:1618–1625
45. Friedman AJ, Lobel SM, Rein MS, Barbieri RL (1990) Efficacy and safety considerations in women with uterine leiomyomas treated with gonadotropin-releasing hormone agonist: the estrogen threshold hypothesis. Am J Obstet Gynecol 163:1114–1119
46. Friedman AJ, Barbieri RL, Doublet PM, Fine C, Schiff I (1989) A randomized, double-blind trial of gonadotropin releasing hormone agonist (leuprolide) with or without medroxyprogesterone acetate in the treatment of leiomyomata uteri. Fertil Steril 49:404–409
47. Palomba S, Russo T, Orio F jr, Sammartino A, Sbano FM, Nappi C, Colao A, Mastrantonio P, Lombardi G, Zullo F (2004) Lipid, glucose, and homocysteine metabolism in women treated with a gonadotropin-releasing hormone agonist with or without raloxifene. Hum Reprod 19:415–421
48. Carr BR, Marshburn PB, Weatherall PT (1993) An evaluation of the effect of gonadotropin-releasing hormone analog and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double-blind, placebo-controlled, crossover trial. J Clin Endocrinol Metab 76:1217–1223
49. Nakayama H, Yano T, Sagara Y, Kikuchi A, Ando K, Wang Y, Watanabe M, Matsumi H, Osuga Y, Momoeda M, Taketani Y (1999) Estriol add-back therapy in the long acting gonadotropin-releasing hormone agonist treatment of uterine leiomyomata. Gynecol Endocrinol 13:382–389
50. Modelska K, Cummings S (2002) Tibolone for postmenopausal women: systematic review of randomized trials. J Clin Endocrinol Metab 87:16–23
51. Volker W, Coelingh Bennink HJ, Helmond FA (2001) Effects of tibolone on the endometrium. Climacteric 4:203–208
52. Gregoriou O, Vitoratos N, Papadias C, Konidaris S, Costomenos D, Chryssikopoulos A (1997) Effect of tibolone on postmenopausal women with myomas. Maturitas 27:187–191
53. De Aloysio D, Altieri P, Pennacchioni P, Salgarello M, Ventura V (1998) Bleeding patterns in recent postmenopausal outpatients with uterine myomas: comparison between two regimens of HRT. Maturitas 29:261–264
54. Fedele L, Bianchi S, Raffaelli R, Zanconato R (2000) A randomized study of the effects of tibolone and transdermal estrogen replacement therapy in postmenopausal women with uterine myomas. Eur J Obstet Gynecol Reprod Biol 88:91–94
55. Palomba S, Pellicano M, Affinito P, Di Carlo C, Zullo F, Nappi C (2001) Effectiveness of short-term administration of tibolone plus gonadotropin-releasing hormone analogue on the surgical outcome of laparoscopic myomectomy. Fertil Steril 75:429–433
56. Palomba S, Affinito P, Tommaselli GA, Nappi C (1998) A clinical trial on the effects of tibolone association with gonadotropin-releasing hormone analogues for the treatment of uterine leiomyomata. Fertil Steril 70:111–118
57. Palomba S, Affinito P, Di Carlo C, Bifulco G, Nappi C (1999) Long-term administration of tibolone plus gonadotropin-releasing hormone agonist for treatment of uterine leiomyomas: effectiveness and effects on vasomotor symptoms, bone mass, and lipid profile. Fertil Steril 72:889–895
58. Somekawa Y, Chiguchi M, Ishibashi T, Wakana K, Aso T (2001) Efficacy of ipriflavone in preventing adverse effects of leuprolide. J Clin Endocrinol Metab 86:3202–3206
59. Black LJ, Sato M, Rowley ER, Magee DE, Bekele A, Williams DC, Cullinan GJ, Bendele R, Kauffman RF, Bensch WR (1994) Raloxifene (LY139481 HCL) prevents bone loss and reduces serum cholesterol without causing uterine hypertrophy in ovariectomized rats. J Clin Invest 93:63–69
60. Fuchs-Young R, Howe S, Hale L, Miles R, Walker C (1996) Inhibition of estrogen stimulated growth of uterine leiomyomas by selective estrogen receptor modulators. Mol Carcinog 17:151–159
61. Bryant HU, Glasebrook AL, Yang NN, Sato M (1996) A pharmacological review of raloxifene. J Bone Miner Metab 14:1–9
62. Porter KB, Tsibris JC, Porter GW, Fuchs-Young R, Nicosia SV, O'Brien WF (1998) Effects of raloxifene in a guinea pig model for leiomyomas. Am J Obstet Gynecol 179:1283–1287
63. Walker CL, Burroughs KD, Davis B, Sowell K, Everitt JI, Fuchs-Young R (2000) Preclinical evidence for therapeutic efficacy of selective estrogen receptor modulators for uterine leiomyoma. J Soc Gynecol Investig 7:249–256
64. Palomba S, Orio F Jr, Morelli M, Russo T, Pellicano M, Zupi E, Lombardi G, Nappi C, Benedetti Panici PG, Zullo F (2002) Raloxifene administration in premenopausal women with uterine leiomyomas: a pilot study. J Clin Endocrinol Metab 87:3303–3308
65. Palomba S, Russo T, Orio F Jr, Tauchmananovà L, Zupi E, Benedetti Panici PG, Nappi C, Colao A, Lombardi G, Zullo F (2002) 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 17:3213–3219
66. Palomba S, Orio F jr, Morelli M, Russo T, Pellicano M, Nappi C, Mastrantonio P, Lombardi G, Colao A, Zullo F (2002) Raloxifene administration in women treated with gonadotropin releasing hormone agonist for uterine leiomyomas: effects on bone metabolism. J Clin Endocrinol Metab 87:4476–4481
67. Palomba S, Orio F jr, Russo T, Falbo A, Amati A, Zullo F (2004) Gonadotropin-releasing hormone agonist with or without raloxifene: effects on cognition, mood, and quality of life. Fertil Steril (in press)
68. Palomba S, Orio F Jr, Russo T, Falbo A, Cascella T, Doldo P, Nappi C, Lombardi G, Mastrantonio P, Zullo F (2004) Long-term effectiveness and safety of GnRH agonist plus raloxifene administration in women with uterine leiomyomas. Hum Reprod 19:1–7
69. Di Carlo C, Palomba S, Tommaselli GA, Guida M, Di Spiezio Sardo A, Nappi C (2001) Use of leuprolide acetate plus tibolone in the treatment of the severe premenstrual syndrome. Fertil Steril 75:380–384
70. Modelska K, Cummings S (2002) Tibolone for postmenopausal women: systematic review of randomized trials. J Clin Endocrinol Metab 87:16–23
71. Huirne JA, Lambalk CB (2001) Gonadotropin-releasing-hormone-receptor antagonists. Lancet 358:1793–1803
72. Kettel LM, Murphy AA, Morales AJ, Rivier J, Vale W, Yen SS (1993) Rapid regression of uterine leiomyomas in response to daily administration of gonadotropin-releasing hormone antagonist. Fertil Steril 60:642–646
73. Felberbaum RE, Germer U, Ludwig M, Riethmuller-Winzen H, Heise S, Buttge I, Bauer O, Reissmann T, Engel J, Diedrich K (1998) Treatment of uterine fibroids with a slow-release formulation of the gonadotrophin releasing hormone antagonist Cetrorelix. Hum Reprod 13:1660–1668
74. Gonzalez-Barcena D, Alvarez RB, Ochoa EP, Cornejo IC, Comaru-Schally AV, Engel J, Reissmann T, Riethmuller-Winzen H (1997) Treatment of uterine leiomyomas with luteinizing hormone-releasing hormone antagonist Cetrorelix. Hum Reprod 12:2028–2035
75. Hara T, Araki H, Kusaka M, Harada M, Cho N, Suzuki N, Furuya S, Fujino M (2003) Suppression of a pituitary-ovarian axis by chronic oral administration of a novel nonpeptide gonadotropin-releasing hormone antagonist, TAK-013, in cynomolgus monkeys. J Clin Endocrinol Metab 88:1697–1704