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GnRH agonist therapy before myomectomy or hysterectomy

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Uterine leiomyomata, also known as fibroids or myomas, are the most common pelvic tumor, found in at least 20% to 25% of women by the age of 35[1] and in more than 50% of all women.[2] Though the majority of myomas (50%–80%) are asymptomatic, they can be the cause of pelvic pressure and pain, excessive menstrual bleeding, spontaneous abortion, and infertility.[3] The standard treatment for symptomatic myomas has been surgical; approximately 40% of abdominal hysterectomies are performed for the treatment of myomas.[4] In those women who wish to preserve fertility, myomectomy is performed. The purpose of this manuscript is to review the use of gonadotropin-releasing hormone (GnRH) agonist therapy before myomectomy and hysterectomy.

Effects of GnRH agonists on uterine myomas

Though the pathogenesis of uterine myomas is not well understood, it is known that these tumors are steroid responsive. Myomas are rarely present before menarche and typically regress after menopause when sex steroid levels are low. Estrogen and progesterone receptors are present in myomas[5] and appear to be over expressed in myoma tissue compared with normal myometrium.[6] Myomas also possess greater aromatase activity than the surrounding myometrium.[7] This increase in local estrogen concentration further contributes to the growth advantage that the myomas possess.[8] In addition to ovarian steroids, endogenous expression of several growth factors, cytokines, and receptors appear to play a role in myoma growth.[9]

As myoma growth appears greatest when sex steroid levels are high, it follows that medications that reduce the levels of gonadal steroids are options for the treatment of uterine myomas. Though oral contraceptives and progestins have been demonstrated to reduce menstrual blood loss, they have not been shown consistently to cause myoma shrinkage. Gonadotropin-releasing hormone (GnRH) agonists, which induce a hypoestrogenic state,[10] were first used over 2 decades ago to treat uterine myomas.[11] The proband patient experienced a 77% reduction in myoma volume, cessation of excessive bleeding, and an increase in hemoglobin concentration from 7.4 to 12.8 g/dL. There appear to be several mechanisms by which GnRH agonists induce a reduction in myoma size. The greatest benefit is derived from the hypoestrogenic state induced with therapy. Treatment with GnRH agonists also result in a reduction in the expression of insulin-like growth factor (IGF)-I, IGF-II, epidermal growth factor (EGF), and EGF receptor mRNA and protein (Table 1), transforming growth factor β (TGFβ), and TGFβ receptor mRNA and protein.[12–15] Myoma tissue also has GnRH receptors, which may play a role in myoma regression in women receiving GnRH agonist therapy.[16]

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Table 1 Effect of GnRH agonists on epidermal growth factor binding to myometrium and myoma

Patients	EGF binding to myoma (fmol/mg protein)	EGF binding to myometrium (fmol/mg protein)	p
Treated (n =12)	10 (5.5–45.7)	19.8 (7.7–47)	<.01
Untreated (n = 12)	24 (8.2–44.2)	17.5 (6.7–39)	<.01

EGF = epidermal growth factor; GnRH = gonadotropin-releasing hormone.
Data from reference 15.

Since the initial report, multiple uncontrolled studies have demonstrated the efficacy of GnRH agonists in the reduction of uterine volume, resolution of anemia, and induction of amenorrhea. The reported reduction of uterine volume with the use of a GnRH agonist ranges between 35% and 65%. Though larger myomas appear to experience a greater reduction in size than smaller ones,[17,18] the response of an individual myoma is more difficult to predict.[19–24] It was postulated that the variability in response was secondary to heterogeneity of myoma composition, with a lack of myoma shrinkage occurring in myomas that were composed primarily of fibrous tissue and therefore no longer hormonally active. In patients with menorrhagia, hematocrit levels typically increase with GnRH agonist therapy.[21,22]

A number of randomized, double-blind, placebo-controlled trials confirmed the efficacy of GnRH agonists in achieving reduction of uterine volume and improvement in symptoms.[25–28] In the largest of these trials, the use of leuprolide acetate (LA), 3.75 mg given intramuscularly (IM) every 4 weeks, was associated with a reduction in mean uterine volume (calculated as a prolate ellipsoid by the formula $\Pi/6$ [length $\times$ width $\times$ depth]) of 36% and 45% after 12 and 24 weeks of therapy, respectively (Figure 1).[26] Patients treated with placebo had increases in mean uterine volume of 16% after 12 weeks and 5% after 24 weeks. Thirty-eight percent of LA-treated patients had a more than 50% reduction in uterine volume and 77% a more than 25% reduction in uterine volume at 24 weeks of therapy. The majority of patients had resolution or improvement of their myoma-related symptoms. In patients with menorrhagia, treatment with LA resulted in a significant increase in hematocrit from 37.3 $\pm$ 0.6% to 38.9 $\pm$ 0.6% (p = .01). This increase in hematocrit was not seen in the placebo treated group.

Once it was known that GnRH agonists were effective in causing myoma shrinkage, it became important to assess the impact of the type and dosage of GnRH agonist as well as appropriate duration of therapy. All clinically available GnRH agonists are capable of producing profound pituitary and gonadal suppression. Hence, they all should be beneficial in the treatment of uterine myomas. Studies evaluating buserelin, histrelin, goserelin, nafarelin, and triptorelin have all demonstrated reduction in uterine volume and improvement in symptoms[17–22,27] (Table 2). A small randomized trial comparing intranasal buserelin with subcutaneous goserelin found no difference in response after 6 months of treatment.[29] There are no other data comparing type of GnRH agonist and method of administration on myoma response. Hence, it is not certain that they have equivalent efficacy. Though inadequate pituitary/gonadal suppression may reduce the efficacy of a GnRH agonist, it does not appear that increasing the dose results in a greater effect on myoma size. Dosages greater than 3.75 mg LA given monthly for 3 months do not result in a greater decrease in the size of the uterine myomas.[30] It has been reported that the administration of 1.88 mg of LA for 24 weeks resulted in an equivalent reduction in uterine volume as did treatment with 3.75 mg LA (41% and 45%, respectively [Figure 2]).[31] In contrast, it was found that use of a high-dose long-acting depot preparation was associated with a greater reduction in myoma size than a standard monthly injection.[32] The initial studies evaluated the use of GnRH agonists for 24 weeks. Most studies demonstrated that the greatest reduction in uterine size occurred within the first 12 weeks of therapy with minimal additional benefit derived from longer treatment[18–23,27] (Figure 1). Gonadotropin-releasing hormone agonist therapy with LA typically administered as 3.75 mg IM monthly, for three doses.

Side effects of GnRH agonist therapy

The side effects and risks associated with GnRH agonist administration are related to the induced hypoestrogenic state. Over 90% of women treated with GnRH agonist experience vasomotor symptoms.[33] Approximately half will also experience insomnia, mood swings, headaches, and vaginal dryness.[33] Patients' perception of memory impairment has been reported to decrease during 24 weeks of GnRH agonist therapy with improvement when the GnRH agonist was halted. This impairment was not related to

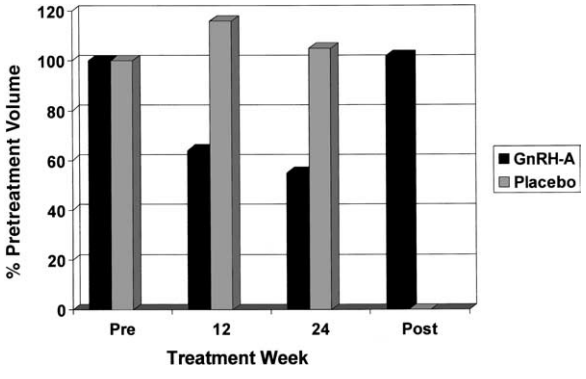

Figure 1 Change in uterine volume in patients taking gonadotropin-releasing hormone agonist (GnRH-a) or placebo. Data from reference 26.