Use of a Gonadotropin-releasing Hormone Agonist to Manage Perimenopausal Women With Symptomatic Uterine Myomas

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SUMMARY

Objective: To determine the acceptability and effectiveness of a gonadotropin-releasing hormone (GnRH) agonist for the treatment of perimenopausal women with symptomatic uterine myomas.

Materials and Methods: The participants included 43 women with symptomatic myomas who wished to retain their uteri. All the women were older than 45 years old, agreed to use the GnRH agonist for menopause induction, and were without any underlying malignancy. They were treated with six courses of GnRH agonist between 2004 and 2005. The definition of re-intervention included: (1) surgical intervention, such as hysterectomy, myomectomy or laparoscopic uterine vessel occlusion, or (2) modification of GnRH agonist use. Modification of GnRH agonist use included either failure to complete a 6-month GnRH agonist treatment course, or re-use of GnRH agonist with/without interruption of continuity. Failure was defined as women who underwent surgical intervention or failed to complete the 6-month GnRH agonist treatment. Evaluations were performed every 6 months, for up to 2 years.

Results: Re-intervention rates were 14.0% ($n=6$), 23.3% ($n=10$) and 32.6% ($n=14$), and failure rates were 7.0% ($n=3$), 11.6% ($n=5$) and 16.3% ($n=7$), at the end of the 6-, 12- and 24-month follow-up periods, respectively. Three patients failed to complete the 6-month GnRH agonist treatment, and four received surgical interventions.

Conclusion: More than 80% of women in this study benefited from the use of GnRH agonist to produce menopause, suggesting that this can be an alternative choice for managing perimenopausal women with symptomatic uterine myomas. [*Taiwan J Obstet Gynecol* 2009;48(2):133–137]

Key Words: anemia, gonadotropin-releasing hormone agonist, perimenopause, uterine myoma

Introduction

Uterine myomas represent the most common benign tumors of the female reproductive system [1,2]. They are mostly asymptomatic [3], and expectant management is, therefore, a common choice [4]. Some myomas, however, can cause symptoms and require treatment [5,6]. For women who wish to retain their childbearing potential, organ-preserving strategies, such as myomectomy, uterine artery ligation or embolization, focal ultrasound surgery, or various kinds of medical treatment, have been the preferred treatments [7–12]. Hysterectomy is still considered to be the treatment of choice in women with symptomatic uterine myomas who have completed their child bearing [13]. However,

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the uterus has been psychologically regarded as a regulator and controller of important physiologic functions, a sexual organ, a source of energy and vitality, and a maintainer of youth and attractiveness [14].

Reproductive sex hormones such as estrogen and progesterone appear to be critical factors related to uterine myomas. Evidence for this includes the fact that: (1) myomas are rarely observed before puberty; (2) they are most prevalent during the reproductive years, and regress after menopause; and (3) factors that increase overall lifetime exposure to estrogen, such as obesity and early menarche, increase the incidence of myomas [15]. This provides us with the possibility of manipulating sex hormones when treating women with symptomatic uterine myomas. However, because the effects of medical treatment are often transient [15] and the symptoms and tumor frequently recur after medication is stopped [16], the use of medical treatment for symptomatic uterine myomas is limited [17,18].

Although medical treatment is seldom considered a definitive treatment, it may be beneficial in a given population; women who are near menopausal status (age ≥ 45 years, defined as perimenopausal) with symptomatic uterine myomas might gain from medical treatment [19,20]. Many drugs are currently available for the management of symptomatic uterine myomas, including gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, the progesterone-mediated intrauterine system, selective estrogen receptor modulators, selective progesterone receptor modulators, androgen-mediated therapy, growth factor-mediated therapy, and others [15]. Among these medical treatments, the use of GnRH agonists is possibly one of the best choices. Some perimenopausal women might transit to natural menopause in an unexpectedly short period, and the use of a GnRH agonist, leading to a natural menopause, is a rational choice. In this study, we explored the effectiveness and limitations of a GnRH agonist for the management of perimenopausal women with symptomatic uterine myomas.

Materials and Methods

Between January 2004 and December 2005, women with symptomatic uterine myomas scheduled for uterine-sparing treatment were invited to participate in the present study. All the uterine-sparing treatments used for symptomatic uterine myomas were well-accepted procedures in our hospital. They included myomectomy (performed by traditional exploratory laparotomy, mini-laparotomy, ultramini-laparotomy, laparoscopy or hysteroscopy), laparoscopic uterine vessel occlusion (LUVO), combination therapy, and medical treatment, including GnRH agonists, progestins, nonsteroidal anti-inflammatory drugs, or pure consultation and follow-up [5,6,10–12,15]. All patients had uterine fibroids with symptoms comprising either menstrual problems, such as menorrhagia and pain, or compression syndrome, including a bulge-like sensation and frequency. These women were informed that they could choose to be treated with any one of the above-mentioned procedures, based on their preference.

This study was designed to assess the effectiveness and limitation of a GnRH agonist for the treatment of fibroids in older women (age ≥ 45 years). Inclusion criteria were: agreeing to use a GnRH agonist for menopause induction for at least 6 months without surgical intervention, no underlying malignancy, an initial strong willingness to avoid surgical treatment if possible, and commitment to completing a thorough, 2-year follow-up record. Surgical interventions included hysterectomy, myomectomy, LUVO or uterine artery embolization. A total of 43 patients were included, and all of them received monthly treatment with a depot GnRH agonist (leuprorelin; Leuplin-Depot; Takeda Pharmaceuticals, Osaka, Japan).

Leiomyoma-related symptoms, including either menstrual problems such as menorrhagia and pain, or compression syndrome (including a bulge-like sensation and frequency), were assessed using a five-point scale to rate changes in symptoms relative to baseline. An initial score of 3 was given if the symptom was present in these women, and subsequent scores ranged from 1 (marked exacerbation), 2 (slight exacerbation), 3 (consistent with the baseline), 4 (slight improvement), to 5 (significant improvement). The same five-point scale was also used to record satisfaction with a baseline score of 3, and ranging from 1 (very dissatisfied) to 5 (very satisfied).

At each follow-up evaluation (6, 12 and 24 months), any medical or surgical treatment of the myoma was recorded. Re-intervention included: (1) failure, defined by the need for hysterectomy, myomectomy, uterine vessel occlusion for uterine myomas, or discontinuation of GnRH agonist treatment (treatment for < six cycles) due to poor patient compliance; and (2) fulfillment of the criteria of success, such as re-use of GnRH agonist after completing the 6-month GnRH agonist treatment, and continuous use of GnRH agonist for 24 months without cessation.

SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) was used to analyze patient data. Paired *t* tests were used to analyze changes in each score from baseline. Statistical significance was defined as $p < 0.05$.

Results

The mean age of the patients was 47.4 ± 1.9 years. The mean baseline hemoglobin level was 9.2 ± 1.9 g/dL. Additional baseline characteristics are provided in Table 1.

In this study, continuous vaginal spotting was noted in > 50% of the women ($n = 24$) after the first dose of GnRH agonist. However, after the second dose (1 month later), the incidence of continuous vaginal spotting had decreased to 21% ($n = 9$), and after the third dose, nearly all women had amenorrhea (98%, $n = 42$). Three patients (7%) stopped GnRH agonist treatment after the third dose owing to intolerable or severe climacteric symptoms. Although additional hormone supplements were prescribed at the second dose of GnRH agonist, these patients decided to stop any further treatment. Finally, all women had amenorrhea by the sixth dose when they continued with GnRH agonist treatment during the study period.

The re-intervention rate was 14% ($n = 6$) at the end of the 6-month follow-up, including three patients who failed to complete the 6-month GnRH agonist treatment, and three patients who continued to receive GnRH agonist monthly treatment after the 6-month period. The re-intervention rate increased to 23.3% ($n = 10$) at the end of the 12-month follow-up. This included the above-mentioned patients ($n = 6$), as well as two patients who were treated with re-administration of the GnRH agonist, one who underwent LUVO, and one who underwent myomectomy. At the end of the 24-month follow-up, the re-intervention rate was 32.6% ($n = 14$). This included the previous patients, plus a further two who were re-administered GnRH agonist, and two who underwent hysterectomy. The symptom change and satisfaction scores improved significantly between the successive 6-month follow-ups (at the end of 6, 12 and 24 months) and baseline ($p = 0.001$), suggesting that the women who were treated with the GnRH agonist benefited from symptom improvement, with a resultant high level of satisfaction. A summary of the clinical outcomes is presented in Table 2.

Table 1. Clinical characteristics of the patients ($n = 43$)*

Age (yr)	47.4 ± 1.9
Body mass index	22.46 ± 1.56
Baseline hemoglobin level (g/dL)	9.2 ± 1.9
Symptom	
Pain	8 (18.6)
Menorrhagia	30 (69.8)
Bulge sensation	17 (39.5)
Frequency	15 (34.9)

**Data are presented as mean ± standard deviation or n (%).*

Discussion

GnRH agonists are among the most effective and well-accepted drugs for the management of myomas. They are analogs of endogenous GnRH and bind to pituitary GnRH receptors (GnRH-R), resulting in the synthesis and release of luteinizing hormone and follicle-stimulating hormone. Compared with GnRH, GnRH agonists have a longer half-life, leading to continuous exposure of GnRH-R under the activity of GnRH agonists. Downregulation of the GnRH-R consequently results in a decreased level of gonadotropin and a

Table 2. Characteristics of subjects ($n = 43$) during follow-up*

	Follow-up			
	Baseline	6 months	12 months	24 months
Re-intervention	0 (0)	6 (14)	10 (23.3)	14 (32.6)
Hemoglobin level (g/dL)	9.16 ± 2.18	12.87 ± 0.55	11.22 ± 0.22	11.16 ± 0.27
Symptom†				
Pain	0.56 ± 1.18	0.91 ± 0.29‡	0.81 ± 0.26‡	0.79 ± 0.26‡
Menorrhagia	2.09 ± 1.39	3.49 ± 0.35‡	2.74 ± 0.21‡	2.88 ± 0.34‡
Bulge sensation	1.19 ± 1.48	1.81 ± 0.35‡	1.65 ± 0.32‡	1.60 ± 0.32‡
Frequency	1.05 ± 1.45	1.58 ± 0.39‡	1.47 ± 0.32‡	1.44 ± 0.32‡
Amenorrhea	0 (0)	40 (93.0)	14 (32.5)	20 (46.5)
Satisfaction†	3.00 ± 0.00	4.44 ± 0.73‡	4.12 ± 0.96‡	4.28 ± 0.98‡
Failure		3 (7.0)	5 (11.6)	7 (16.3)

**Data are presented as n (%) or mean ± standard deviation; †the definitions of symptom (pain, menorrhagia, bulge sensation, frequency) change and satisfaction are available in the text; ‡compared with baseline, all $p < 0.005$.*

suppressed production of ovarian hormones [21]. The administration of GnRH agonists leads to extremely low "pseudomenopausal" or "pseudopremenarchal" estradiol levels, resulting in amenorrhea.

In terms of alleviating menorrhagia, it has been reported that bleeding problems or related anemia were controlled in women after the first month of GnRH agonist treatment [22,23].

Pain and pressure symptoms were reported to be relieved within the first 3 months of treatment. This effect can be achieved within the first 12 weeks of therapy, because it is considered to be a consequence of reducing the size of the uterus and myoma [24]. In addition, it has been reported that the effect of GnRH agonists on reducing myoma size is transient; reversal of estrogen deprivation occurs about 4 weeks after discontinuation of the GnRH agonist [25] and most myoma nodules returned to their initial size within about 6 months after discontinuation of treatment. The rate of enlargement was then rapid compared with natural enlargement [22], and regrowth of the uterus and myomas leads to a recurrence of the initial symptoms [26]. We did not routinely monitor uterine and myoma size in the current study, so were unable to assess any changes. However, all but three of the women (who failed to complete the 6-month GnRH agonist treatment) were satisfied with their symptom relief, including pain, bulging sensation and frequency, especially after the initial 6 months. The symptom improvement was maintained up to the end of the 12- and 24-month follow-ups (Table 2), suggesting that the use of GnRH agonist treatment for perimenopausal women with symptomatic uterine myomas should be considered before choosing a more invasive surgical intervention.

The significant disadvantages of GnRH agonists include hypoestrogenism-related effects resembling postmenopausal climacteric disturbances and bone loss [27]. Partial restoration of the estrogenic state by reduced-dose therapy or steroid "add-back" has been shown to be effective for the relief of annoying side effects, without any loss of the beneficial effects on myoma size and cycle suppression [28,29]. The addition of oral veralipride, a benzamide derivative, can reduce the vasomotor symptoms induced by GnRH agonists [30]. Raloxifene or tibolone may also be used as add-back therapy to prevent bone loss whilst preserving the efficacy of GnRH agonists [31,32]. However, raloxifene did not reduce vasomotor symptoms related to GnRH agonists [31], and could even exacerbate climacteric symptoms [33,34]. In contrast, a significant reduction in hot flushes was observed when tibolone was added to GnRH agonist treatment [32]. Either a lower dose of hormone replacement therapy or use of tibolone can be successfully applied in symptomatic menopausal women [35–39]. In this study, only three women who failed to complete the 6-month GnRH agonist treatment were reported to have intolerable climacteric symptoms. Although add-back therapy was initiated during the third month, the patients were still anxious about the risk of breast cancer and finally decided to stop any medication, except for nonsteroidal anti-inflammatory drugs and iron replacement. In contrast, more than 90% of the perimenopausal women tolerated the treatment well. In addition, three women chose to continue monthly GnRH agonist treatment up to 24 months and two women were re-treated with GnRH agonist 12 months later.

Amenorrhea was reported in only 50% of the women in this study, at the end of the 24-month follow-up period. This was in contrast to the results of Imai et al [19], who found that the depot GnRH agonist, leuprorelin acetate, produced an excellent success rate (>90%) by inducing natural menopause in 19 of 21 perimenopausal women with uterine myomas [19].

In conclusion, more than 80% of women in this study experienced significant symptom relief after treatment with a GnRH agonist. These results indicate that GnRH agonists should be considered as an option for the management of perimenopausal women with uterine myomas, in order to reduce the use of more invasive surgical interventions.

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