

The effects of add-back therapy with tibolone on myoma uteri

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Summary

In this prospective, randomized, double-blind study, we evaluated the effects of tibolone therapy in association with preoperative gonadotropin releasing hormone agonist (GnRHa) therapy on the reduction of myoma volume.

Twenty patients with myoma uteri were divided into two groups. Group I was given monthly triptoreline (3.75 mg every 28 days IM) treatment for six months. As for group II, tibolone was added on to this treatment. For all of the patients, physical examinations, pelvic ultrasonography, and hormone analyses were carried out and the myoma volume was measured by ultrasonography. The patients were called every month and physical examination, ultrasonography and hormone analyses were repeated. Side-effects were recorded. The SPSS/PC 6.0 program was used for statistical analysis. Statistical significance was defined as a $p < 0.05$. The results are expressed as means \pm SD.

While the average volume of myoma was $72.97 \pm 68.5 \text{ cm}^3$ in group I, $78.83 \pm 74.1 \text{ cm}^3$ in group II before treatment; it was reduced to $29.91 \pm 27.8 \text{ cm}^3$ in group I at the end of six months of treatment. Reductions of 59.6% in group I and 63.9% in group II were determined, however the difference was not statistically significant ($p > 0.05$). At the beginning the level of serum estradiol was $65.4 \pm 22.3 \text{ pg/ml}$ in group I which decreased to $37.2 \pm 4.2 \text{ pg/ml}$ by the end of the first month. Amenorrhea occurred in six patients after the second injection and four patients after the third injection in group I. Whereas the level of estradiol was $60.9 \pm 19.5 \text{ pg/ml}$ in group II at the beginning, it was reduced to $40.5 \pm 6.2 \text{ pg/ml}$ by the end of the first month. Amenorrhea occurred in four patients after the second injection and four patients after the third injection in group II. In group I the patients had the problem of flushing (80%), vaginal dryness (50%), and night sweats (30%). In group II these rates were 30%, 20%, and 20%, respectively. Triptoreline is a GnRHa which has been found to be effective in reducing myoma volume, but this effect could not be deactivated with tibolone. However, a decrease was observed in the side-effects resulting from hypoestrogenism.

Key words: Myoma uteri; Triptoreline; Tibolone; Preoperative gonadotropin releasing hormone agonist therapy; Side-effects.

Introduction

Myoma uteri is seen in 20-25% of women in reproductive age. Defects of menstrual cycles, pain and infertility can be seen. In the symptomatic events, standard treatment is surgery and according to age and the wish of having a child, conservative or radical surgery can be performed. Estrogen and progesterone receptors are found in the tissue of myoma. Reduction in the volume of the myoma is seen as a result of decreased levels of steroids after menopause. Therefore, the volume of the myoma can be reduced by creating postmenopausal estrogen levels using gonadotropin releasing hormone agonist (GnRHa) continually. However, side-effects resulting from hypoestrogenism disturb the patients [1-3].

The aim of this study was to research the effect created by adding tibolone to triptoreline, a GnRHa, in reducing the volume of the myoma in patients undergoing surgery for myoma uteri.

Materials and Methods

This randomized, double-blind and prospective study was performed at the Department of Obstetrics and Gynecology of Dicle University. Twenty patients with myoma uteri were divided into two groups. Seven patients in group I had abnor-

mal uterine bleeding and three patients were infertile, whereas, six patients in group II had abnormal uterine bleeding, two patients had secondary dysmenorrhea and two patients were infertile. The patients in group I (n: 10) received triptoreline (decapeptyl) 3.75 mg every 28 days IM, treatment for six months. The patients in group II (n: 10) received triptoreline, as described above, plus tibolone per os at a dose of 2.5 mg/d for six months. The first injections were performed in the early follicular phase of the cycle (2-3 d), and tibolone was started on the same day. Surgical treatment was performed one month after the last injection.

For all of the patients, physical examinations, pelvic ultrasonography, hormone analyses were carried out and the volume of the myoma was measured by ultrasonography. The Toshiba 270 SSA was used for ultrasonographic evaluation. The volume of the myoma was calculated by the ellipsoid formula: $D_1 \times D_2 \times D_3 / 4/3 \times \pi \times 0.52$ [4]. The patients were called every month and physical examination, ultrasonography and hormone analyses (FSH, LH, E_2) were repeated. Side-effects were recorded.

The Statistical Package for the Social Sciences (SPSS for Windows) PC 6.0 program was used for statistical analysis. The Mann-Whitney U test was used to compare two independent samples. Statistical significance is defined as $p < 0.05$ and the results are expressed as means \pm SD.

Results

The ages of the patients were between 24-40. Mean age was 33 ± 4 in group I and 33 ± 5 in group II. The hormone values of the patients are given in Table I.

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Table 1. — Levels of FSH, LH and E₂ in both groups by months.

	GROUP I	GROUP II	GROUP I	GROUP II	GROUP I	GROUP II
	FSH(miu/ml)	FSH(miu/ml)	LH(miu/ml)	LH(miu/ml)	E ₂ (pg/ml)	E ₂ (pg/ml)
Preface	12.5±3.9	10.1±4.9	9.3±6.8	8.7±7.4	65.4±22.3	60.9±19.5
1th mo	5.7±2.5	6.3±2.5	6.3±2.7	6.8±4.5	37.2±4.2	40.5±6.2
2nd mo	2.7±1.8	3.3±1.6	4.1±1.7	3.5±1.8	31.4±9.8	34.5±5.4
3 rd mo	2.8±1.6	3.1±2.2	3.2±1.1	2.8±1.5	34.7±7.3	31.7±10.3
4 th mo	2.5±1.4	2.0±1.7	1.7±1.3	1.4±1.2	36.3±6.2	30.5±10.4
5 th mo	1.5±1.6	1.8±1.5	1.5±0.9	1.4±1.2	34.5±8.7	29.3±9.8
6 th mo *	2.1±1.1	1.6±1.2	1.7±0.3	1.2±0.5	35.1±6.2	31.6±10.4

* No differences were observed between levels of FSH, LH and E₂ in either group ($p > 0.05$)

Table 2. — Volume and reduction (%) of uterine myomas in both groups.

	GROUP I	GROUP II	GROUP I	GROUP II	
	\bar{X} (Volume) ± SD	\bar{X} (Volume) ± SD	Reduction (%)	Reduction (%)	p
Before treatment	72.9±68.5	78.8±74.1	—	—	
1 st mo	51.2±54.2	52.5±57.4	29.9	33.4	
2 nd mo	41.7±46.3	40.5±47.7	42.8	48.6	>0.05
3 rd mo	35.2±45.8	30.1±47.5	51.7	61.8	
4 th mo	31.6±32.9	28.2±31.4	56.7	64.2	
5 th mo	29.9±27.8	28.4±31.7	59.6	63.9	

Serum estradiol levels in group I decreased to 37.2 ± 4.2 pg/ml at the end of the first injection. As for group II, it decreased to 40.5 ± 6.2 to pg/ml. Both FSH and LH levels of each group decreased to < 5 mIU/ml at the end of the second month. In the myoma volume of group I a decrease of 29.9% after the first injection and 59.6% at the end of the sixth month was seen. However, in group II decreases of 33.4% and 63.9% were seen, respectively. The difference was not significant (Table 2). Amenorrhea occurred in six patients after the second injection and four the after in third injection in group I. However, amenorrhea occurred in four patients after the second injection and four the after in third injection in group II (Figure 1). In group I, 80% of the patients had the problem of flushing and 50% vaginal dryness and night sweats. In group II these were 30%, 30%, and 30%, respectively (Figure 2). None of the patients had bleeding that required urgent surgical treatment.

Discussion

Myoma uteri is the most common benign tumor of the uterus, and causes menorrhagia and pressure to the pelvic area. If another cause cannot be found for infertility, a chance for pregnancy can arise as a result of constrictive surgery [4, 5]. As a result of GnRHa, hypoestrogenism is

created and myoma volume can be reduced. Stovall *et al.* [6] stated that in patients with symptomatic myoma, uterine volume was reduced as a result of GnRHa before hysterectomy, and the chance of vaginal hysterectomy rose while the hospitalization period and intraoperative bleeding decreased. Candiani *et al.* [7] found that by using gosereline in patients with myoma for six months, the volume of uterine myoma decreased by 49%, and no change was seen in the following months.

In our study the myoma volume of group I was reduced by 29.9% in the first month of treatment, 51.7% in the third month and 59.6% in the sixth month, whereas in group II it was reduced by 33.4% in the first month of treatment, 61.8% in the third month and 63.9% in the sixth month.

It has been reported that the administration of GnRHa leads to the most common side-effects (flushing and vaginal dryness, 97% and 71%, respectively) arising from hypoestrogenism [8, 9]. However, in our study in the group not receiving tibolone, flushing was seen in 80% and vaginal dryness in 50% of the patients.

Friedman *et al.* [9] added estrogen-progesterone or only progesterone to leuprolide acetate after the third month of treatment in order to apply long-term GnRHa treatment (2 years) to patients with myoma and to prevent side-effects due to hypoestrogenism. They observed a 40% decrease of uterine volume in each group in the first three months.

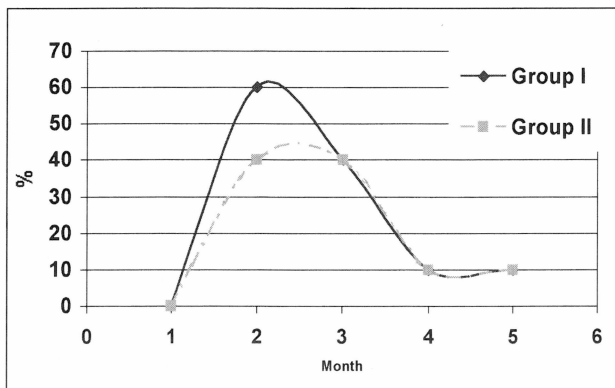


Figure 1. — Time of increasing amenorrhea.

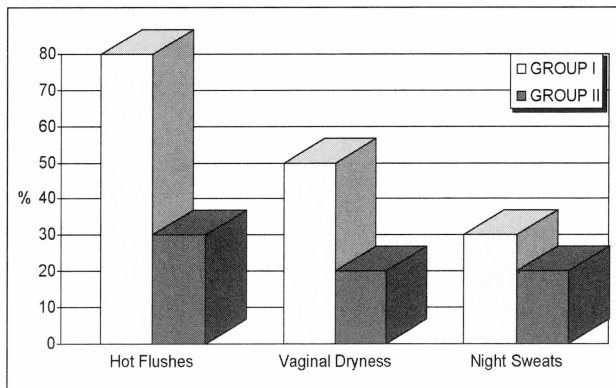


Figure 2. — Side-effects depending on hypoestrogenemia.

There was no change in uterine volume in the group taking estrogen-progesterone in the following period, while in the group taking progestine the uterine volume reached 87% of the first volume. However, in our study tibolone was started on the first day of injection, and there were no differences in uterine volume in the two groups.

Şener *et al.* [10] found no effect from oral conjugate estrogen and medroxyprogesterone acetate used for hormone replacement treatment in patients with myoma in the postmenopausal period on the growth of myoma. Lindsay *et al.* [11] maintained that adding tibolone to triptoreline in endometriosis treatment did not decrease the effect of triptoreline but decreased vasomotor symptoms arising from hypoestrogenism.

Although in our study add-back therapy was begun with the first GnRHa injection, uterine volume was reduced. In group I, 80% of the patients had problems of flushing, 50% vaginal dryness and night sweats while in group II, these were 30%, 30%, and 30%, respectively (Figure 2).

In conclusion, the addition of tibolone for add-back therapy in patients who were given triptoreline for myoma uteri did not deactivate the affect of GnRHa or decrease vasomotor symptoms.

References

- [1] Fedele L., Bianchi S., Raffaelli R., Zanconato G.: "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.*, 2000, 88, 91.
- [2] Friedman A. J., Hoffman D. I., Comire F., *et al.*: "Treatment of leiomyomata uteri with leuprolide acetate depot: A double-blind, placebo-controlled, multicenter study". *Obstet. Gynecol.*, 1991, 77, 720.
- [3] Doren M., Rubig A., Coelingh Bennink H. J., Holzgreve W.: "Impact on uterine bleeding and endometrial thickness: tibolone compared with continuous combined estradiol and norethisterone acetate replacement therapy". *Menopause*, 1999, 6 (4), 299.
- [4] Egarter C., Sator M., Berghammer P., Huber J.: "Efficacy, tolerability, and rare side effects of tibolone treatment in postmenopausal women". *Int. J. Gynaecol. Obstet.*, 1999, 64 (3), 281.
- [5] Garcia C. R., and Tureck R. W.: "Submucosal leiomyomas and infertility". *Fertil Steril*, 1984, 42, 16.
- [6] Stovall T. G., Summit R. L. Jr., Washburn S. A., Ling F. W.: "Gonadotropin-releasing hormone agonist use before hysterectomy". *Am. J. Obstet. Gynecol.*, 1994, 170, 1744.
- [7] Candiani G. B., Vercellini P., Fedele L., Arcaini L., Bianchi S., Candiani M.: "Use of gosereline depot, a gonadotropin releasing hormone agonist, for treatment of menorrhagia and severe anemia in women with leiomyoma uteri". *Acta Obstet. Gynecol. Scand.*, 1990, 69, 413.
- [8] Shaw R. W.: "An open randomized comparative study of effect of gosereline and danazol in treatment of endometriosis". *Fertil Steril*, 1992, 58, 265.
- [9] Friedman A. J., Daly M., Juneau-Norcross M., Gleason R., Rein M. S., Le Boff M.: "Long term medical therapy for leiomyomata uteri: a prospective, randomized study of leuprolide acetate depot plus either estrogen-progestin or progestin 'add-back' for 2 years". *Hum. Reprod.*, 1994, 9, 1618.
- [10] Şener A. B., Seçkin N. C., Özmen S., Gökmen O., Doğu N., Ekici E.: "The effects of hormone replacement therapy on uterine fibroids in postmenopausal women". *Fertil Steril*, 1996, 64, 354.
- [11] Lindsay P. C., Shaw R. W., Bennink H. J., Kicovic P.: "The effect of add-back treatment with tibolone (livial) on patients treated with the gonadotropin-releasing hormone agonist triptoreline (Decapeptyl)". *Fertil Steril*, 1996, 64, 342.

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