Comparison of the effect of gonadotropin-releasing hormone analog (Diphereline) and Cabergoline (Dostinex) treatment on uterine myoma regression

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ABSTRACT

Objective: To investigate the effect of cabergoline (Dostinex, a dopamine agonist) on the myoma growth compared to Diphereline (a gonadotropin-releasing hormone agonist).

Methods: This study took place in the Department of Obstetrics and Gynecology of Tabriz University of Medical Sciences, Tabriz, Iran from July 2004 to December 2005. Fifty women with uterine myoma, who met the criteria of the study thoroughly, were randomly allocated into 2 equal groups to take either Diphereline or Cabergoline. The first Group took 3.75 mg of Diphereline 4 times every 28 days and the second group took 0.5 mg of Cabergoline once a week for 6 weeks.

Results: The Cabergoline was well tolerated and fewer adverse effects were noted. The tumor regressed significantly and volume reduction rate of individual tumor nodule varied from 46-53%. The gonadotropin releasing hormone agonist group all responded to the treatment, and volume reduction rate of the individual tumor nodule varied from 21-97%. The extent of tumor shrinkage was positively correlated to the number of nodules (p=0.881, p<0.005 and 0.701, p<0.005).

Conclusions: In light of therapeutic efficacy and few adverse effects, the dopamine agonists may hold promise as novel treatment modalities for leiomyoma. Further studies are warranted to determine the optimal strategy for the treatment of leiomyoma through these agents.

Saudi Med J 2007; Vol. 28 (3): 445-450

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Received 25th July 2006. Accepted for publication in final form 4th November 2006.

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The uterine leiomyoma, a common pelvic tumor of reproductive age that sometimes causes infertility and a significant morbidity, is a smooth muscle tumor with increased cellularity and hypertrophy of the cells. The growth of uterine leiomyoma depends on the growth-supporting hormones and an adequate blood supply.[1,2] As the role of growth factors in the growth of the leiomyoma is better elucidated, the treatment targeted at the growth factor or its receptor may prove useful. In addition, as the molecular biology and the genetics of the leiomyoma are better understood, newer nonsurgical therapies may be developed. However, medical therapy is the preferred solution for women who wish to preserve their uterus.[3] Studies have demonstrated that monthly administration of a long-acting gonadotropin releasing hormone agonist (GnRHa) reduces the size of the uterine leiomyoma and the levels of ovarian hormones and some growth factors that are required for tumor growth.[4] Although the gonadotropin-releasing hormone (GnRH) is primarily involved in the endocrine regulation of gonadotropin secretion from the pituitary, it has autocrine and paracrine functions throughout the body. The role of GnRH in the extrapitutary sites remains to be fully elucidated.[5] Preoperative administration of GnRH agonists results in 40-60% decrease in the uterine volume through the induction of the cell damage by different mechanisms and can be of value in some clinical situations.[6,7] However, such damage in most of the cells can be just sublethal and reversible.[8,9] Regrowth is experienced within few months and the side effects may limit their extensive use.[6,10] Recent advances in endocrinology open a door for clinical application of hormonal therapy for the treatment of the uterine leiomyoma. The growth factors, such as epidermal growth factor (EFR), receptor of EFR (EFR-R), thrombocytic growth factor (TGF), transforming growth factor beta (TGF-ß), insulin-like growth factor of the first type (ILGF1) and prolactin(PRL) may play roles in the development

of the uterine leiomyoma.[11] The prolactin receptor is encoded by a gene on the 5p13-14 chromosome that is near the gene of the growth hormone receptor. The prolactin receptor belongs to a family of receptors that includes many cytokines and many growth factors, supporting a dual role for prolactin as a classic hormone and as a cytokine.[12] Because of the various forms and functions of prolactin, it is likely that multiple signal mechanisms are involved. Nowak et al after testing a hypothesis showed that PRL acts as a mitogenic growth factor and appears to be an autocrine or paracrine growth factor for both leiomyoma and myometrial cells.[12] The nonsurgical management of uterine leiomyoma should be able to inhibit tumor growth by the autocrine mechanism, tailored to the needs of the women presented with uterine fibroids and geared to alleviate the symptoms. As observed in other studies, GnRH agonists were associated with menopausal symptoms and the time required to achieve a significant decrease in size are limitations to their long-term use. Since surgical excision of the large uterine leiomyoma in premenopausal and infertile women is hazardous, a randomized clinical trial was designed to compare the effect of 2 medications (GnRHa and dopamine agonist) on myoma regression, side effects and explore their correlation with tumor shrinkage caused by the therapy.

Methods. Patients who had uterine myoma nodules larger than 5 cm in diameter with irregular menstrual cycle and candidate for myomectomy at the Alzahra University Hospital (Tabriz, Iran) were prospectively collected from July 2004 to December 2005. The study was reviewed and approved by the institutional review board, and written consent was obtained in accordance with the Human Rights Committee Guidelines of the Hospital. The demographic and other information were abstracted from official records and the related forms were filled in. Fifty women with uterine myoma were enrolled. The participants were assigned randomly to one of 2 treatment groups with one of 2 regimens (Diphereline and Dostinex). For the first group, GnRHa (Diphereline; manufactured by IPSEN Pharma Biotech, France) a 3.75 mg of GnRH-a, was prescribed 4 times every 28 days, and for the second group, 0.5 mg of Cabergoline (Dostinex; manufactured by Pharmacia & Upjohn SPA, Italy), was prescribed once a week for 6 weeks. All patients were asked about the frequency and duration of uterine bleeding, pelvic pain, headache, bone sensivity and pain, hot flushes, and psychological symptoms. A follow-up visit was arranged one week after the termination of the treatment or every time one of the patients showed one of the above mentioned symptoms. A sonography (Hitachi Color Doupler,EUB-525) was conducted at this time and before the treatment in order to asses the rate of myoma shrinkage. The objective findings on pelvic examination and sonographic findings were documented. The results, including fibroma volume at transvaginal ultrasonography (6.5MHz) or a transabdominal probe (3.5MHz) as an adjunct to the transvaginal probe after termination of treatment were compared. In brief, the volumes of leiomyomas were calculated by the formula for the volume of an ellipse (x R1 x R2 x R3/0.52), in which R1, R2, and R3 were the maximal transverse, anteroposterior, and longitudinal lengths of tumor, respectively. In patients with more than one leiomyoma nodule, only the large nodule was selected. The percentage of tumor volume reduction was calculated by 1 (the volume before the treatment/ the volume after the treatment). The tumor volume reduction of more than 20% was deemed as a good response to therapy. The patients who were over 40 years of age, had abnormal uterine pathology, and infection, hypersensivity to any ergot alkaloids, hepatic and renal disorders, history of toxemia of pregnancy, cardiovascular disease, peptic ulcer, and took anti-psychotic medications were excluded. Study population was stratified into groups for analysis: those undergoing the Diphereline administrations, and those undergoing the Cabergoline administration.

The statistical analysis was performed with paired and unpaired t-test to compare the difference between the means. The values were given as median (range) or mean ± SD. The correlation between the variables was calculated by Pearson's correlation test. The statistical analysis was performed using SPSS version 13.0/win statistical software. A value of $p<0.05$ was considered as statistically significant.

Results. Fifty treated patients who had received weekly Cabergoline therapy (n=25) and monthly Diphereline therapy (n=25) for uterine leiomyoma regression were evaluated. The statistical data and characteristics of the patients are summarized in **Table 1**. There were no significant differences in the demographic and the statistical data between the 2 groups ($p>0.05$). The analysis of vaginal sonography indicated a progressive decrease in tumor size following both treatments. There was no difference between groups with regard to the mean tumor volume before treatment ($p=0.56$). Diphereline significantly reduced the leiomyoma tumor volume ($t = 5.93$, $df = 24$, $p<0.005$) (**Table 2**). The volume reduction rate of the individual tumor nodule varied from 21-97%. The mean volume of leiomyomas in cabergoline group was also reduced ($t=6.05$, $df=24$, $p<0.05$)(**Table 2**). The tumor regressed significantly in 17 cases and the volume reduction rate of the individual tumor nodule varied from 46-53% after

Table 1 - Demographic characteristics (mean±SD) and comparison of data (unpaired t-test) for the 2 treatment groups (Diphereline [group 1] and Cabergoline [group 2]).

Characteristics	Group 1 (n=25)	Group 2 (n=25)	t	df	*P* value
Age (years)* (unpaired t-test)	29.56±6.33 (18-39)	31.60±3.76 (25-40)	1.38	39.05	0.17
Number of gravida*	1.04±0.93 (0-3)	1.40±0.86 (0-3)	1.41	48	0.16
Number of parity*	0.52±0.65 (0-2)	0.56±0.50 (0-1)	0.24	48	0.81
Number of myoma before treatment*	2.64±1.35 (1-5)	2.56±1.26 (1-5)	0.21	48	0.83
Number of myoma after treatment*	2.60±1.32	2.48±1.22	0.33	48	0.74
Myoma volume before treatment*	200.88±121.22 (32-380)	180.54±125.06 (1-413)	0.58	48	0.56
Myoma volume after treatment*	101.93±67.58 (19-281.2)	85.67±54.06 (3-203)	0.93	48	0.35

*mean±SD, p<0.05 was considered significant, df - degree of freedom

6 weeks. The hormone treatment was well tolerated in Cabergoline group and had fewer side effects (**Table 3**). Five patients had a tumor volume reduction less than 20% and were deemed as poor responders, and 3 cases showed growth promotion. The comparison of pre- and post-treatment groups of treatment is also shown in **Table 2**. The statistical analyses revealed that leiomyomas with Diphereline treatment expressed more shrinkage as compared to Cabergoline (p<0.005) (**Figures 1 & 2**). However, there was no significant difference between mean volume reduction of the leiomyomas in 2 groups (p=0.85). In addition, the extent of the tumor shrinkage was positively correlated with the number of nodules (r=0.881, p<0.005 and r= 0.701, p<0.005). Hot flushes were experienced by more than 88% of the patients, usually in 3-4 weeks after beginning of GnRHa. Fifty-two percent of the patients in GnRHa group and 4% of the patients in Cabergoline group complained from headache. The mood changes, the vaginal dryness, the joint and muscle stiffness, and depression were observed in 8-92 percent of the first group, but not in any patient of the second group. In contrast, Cabergoline induced dizziness, nausea, vomiting in 16-28% of the patients in the first week of treatment. Only one patient discontinued the treatment in the second group (**Table 3**). Cabergoline group had normal menstruation during treatment course, but GnRHa group developed amenorrhea.

Table 2 - Comparison of pretreatment and post-treatment groups with Diphereline (group 1) and Cabergoline (group 2).

Variables	t	df	*P*-value**
Number of leiomyoma			
Group 1†	1	24	0.32
Group 2†	1.44	24	0.16
Volume o f leiomyoma			
Group 1†	5.93	24	<0.005
Group 2†	6.05	24	<0.005
Mean leiomyoma volume reduction between group 1 and group 2*	0.17	48	0.85

†paired t-test, *unpaired t-test, **p<0.05 was considered significant, df - degree of freedom

Discussion. The treatment of uterine myoma in premenopausal women remains a challenge for gynecologists worldwide, despite several different protocols that have been proposed for myoma regression.[1] The effects of monotherapy with GnRHa on leiomyoma growth in premenopausal women remain controversial.[13] Both GnRH agonists and progestational agents are commonly used in order to reduce the size of uterine leiomyomas before surgery.[14] Gonadotropin releasing hormone agonist may not be suitable for long-term treatment of leiomyomas due to inducing the hypo-estrogenic state. In the early studies, it was thought that add-back therapy with medroxy progesterone acetate or ethynil estradiol could prevent the adverse effects caused by hypo-estrogenic state in the preoperative short-term GnRHa therapy, but the risk of osteoporosis and bone fracture were not eliminated.[15] RU-486 and other antiprogesterone drugs have been shown to shrink myomas in clinical trials. The long-

term effect of these agents on leiomyoma however is unknown.[3] Therefore, alternative regimens for this problem have been explored. Alternate regimens that decrease the number of the treatment days and reduce the side effects could also the convenience of therapy. With regard to hormonal therapy, in this study, the treatment with Cabergoline reduced the size of the leiomyoma in premenopausal women. The exact mechanism remains unclear. The number of the reduced receptor and the subsequent ischemic damages in the leiomyoma or the suppression of the receptors could be responsible for the size of the tumor, the clinical response, and the degeneration of the tumor caused by the Cabergoline treatment. Although the finding is reported here for the first time, the baseline finding is in line with the previous research that suggests a role for prolactin on the growth of the leiomyoma.[11] In the present study, it is found that Cabergoline causes shrinkage of the leiomyomas like GnRHa in the premenopausal women. The data in this study shows that the treatment of the uterine leiomyoma with a dopamine agonist is an affordable and valid alternative in the infertile and premenopausal women. In the study of Nowak et al,[11] the authors performed 3 different types of experiments to assess whether exogenous PRL acts as a mitogen for cultured uterine smooth muscle cells or not. They also examined the role of endogenous PRL by assessing the cell number after exposing the cultures to a neutralizing antibody to PRL. Finally, they examined both the fresh tissues and the cultured cells for expression of the PRL receptor messenger ribonucleic acid. They showed that significant suppression in cell number was seen after 5 days of culture for leiomyoma cells but not for the myometrial cells after the treatment with exogenous PRL. Both cell types showed a significant decrease in cell number after the treatment with anti-PRL antibody. They concluded that PRL appears to be an autocrine or paracrine growth factor for both leiomyoma and myometrial cells. However, there are some differences between tissues in their sensitivity to this growth factor.[11] The results from this and other studies prompted the researchers of this study to investigate the effect of weekly administration of Cabergoline in patients with uterine myoma. Weekly regimen was feasible and well tolerated. In this study, statistical analyses revealed that the leiomyomas with diphereline treatment expressed more shrinkage as compared to Cabergoline. In addition, the extent of the tumor shrinkage was positively correlated with the number of nodules in the first and the second groups (**Table 1**). Of note, more hot flushes or hypoestrogenic conditions were found

Table 3 - Incidence of side effects in the 2 groups of treatment with Diphereline (group 1) and Cabergoline (group 2).

Side effects	Percentage of patients reporting adverse symptoms	
	Diphereline (n=25)	Cabergoline (n=25)
Pelvic pain	44	32
Headache	52	4
Dizziness	0	16
Nausea	0	28
Vomiting	0	28
Treatment continuity	100	96
Bone sensitivity	72	0
Hot flushes	88	0
Psychologic signs	52	0
Vaginal dryness	92	0
Muscular stiffness	8	0

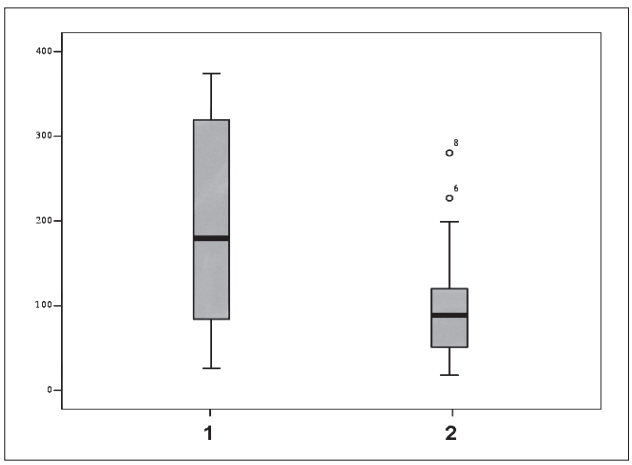

Figure 1 - Myoma volume (ml), before (1) and after (2) treatment in Diphereline group.

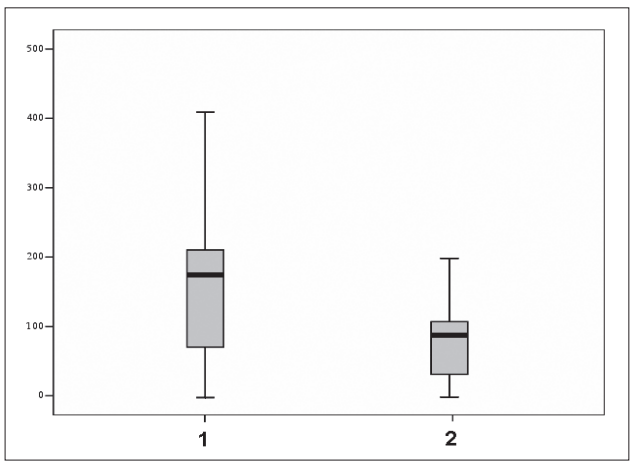

Figure 2 - Myoma volume (ml), before (1) and after (2) treatment in Cabergoline group.

in the Diphereline treated leiomyoma as compared to Cabergoline group. Despite the expression of PRL in glands and vessels, specific phases of the cycle suggests a timely precise physiological action of PRL in these targets; in certain uterine myomas, the PRL-R over expression may contribute to the tumor development because PRL is a potent growth factor. Unusual morphologic features of leiomyomas may be seen in the patients who had been treated preoperatively with GnRH agonists, such as vasculitis and massive lymphoid infiltration.[14] Since GnRH agonists are increasingly being used in the management of uterine leiomyomas; diagnostic confusion may also occur.[13] In a study, authors suggested that it is not hormonal depletion but blood flow reduction that accounts for the tumor shrinkage after GnRHa treatment.[16] Whereas in the dopamine agonist group, the hormonal effect may be responsible for the leiomyoma shrinkage. With regard to hormonal therapy, in this study, the treatment with Cabergoline demonstrated an inhibition of the leiomyoma growth and improvement of the clinical symptoms in the premenopausal women. No serious adverse effects, associated with Cabergoline, were seen. The removal of the myoma was fair and feasible without any strict adhesion. In the present study, the weekly 0.5 mg dose of Cabergoline was not associated with severe side effects. The gastrointestinal symptoms were seen in <28% of cases. Bone sensitivity, hot flushes, vaginal dryness, psychologic signs, and muscular stiffness were not seen (**Table 3**). Although previous reports have demonstrated that monthly GnRHa at a dose of 3.75 mg for 4 months has been well tolerated, a concern remains that this dose may be associated with unacceptable side effects in some patients.[17] Indeed, sometimes, the patients, who have received multiple prior therapies, had side effects related to the long-term treatment.[18] These findings may be diagnostically and therapeutically relevant. Long term treatment with a long acting dopamine agonist is safe, feasible and may result in the higher response rates. Indeed, although the number of cases reviewed were small, they appeared to be an incremental increase in the proportion of the patients who achieved clinical benefit at the higher Cabergoline dose levels. The presence of prolactin-receptor in leiomyomas may allow distinguishing those which respond to Cabergoline. Cabergoline may have an antiproliferative effect on leiomyoma cells via membrane receptors for prolactin and is comparable with GnRHa. Although Cabergoline causes shrinkage of leiomyomas like GnRHa, the effects of the treatment remain to be elucidated.

In conclusion, these findings may have physiological and pathophysiological importance. Weekly Cabergoline is well tolerated and associated with fewer side effects and similar antitumor activity compared with the diphereline. In this study, the use of Cabergoline was a valuable alternative to GnRHa in the treatment of the leiomyoma. Of note, when Cabergoline used for the shrinkage of leiomyoma, in some patients the size of the leiomyoma remained unchanged. These indicated that other growth factors other than PRL-R may be responsible for it. In light of therapeutic efficacy and fewer adverse effects, the dopamine agonists may hold promise as a novel treatment modalities for the leiomyoma. Further studies are warranted to determine the optimal strategy for the treatment of leiomyoma with these agents. Evaluation of histologic changes and examination of tissues and cultured cells for the expression of the PRL receptor messenger ribonucleic acid using the techniques and sonographic changes are suggested.

Acknowledgment. The authors acknowledge with gratitude the participation of patients. In particular, we would like to thank Morteza Ghojazadeh, MD, for performing statistical analysis.

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