GnRH analogs in treating uterine leiomyomata and endometriosis

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Summary: The results of hormonal examinations, measurements of dimensions of the uterus and leiomyomas, body weight, and also frequency of incurred climacteric signs in patients treated with Decapeptyl Depot 3.75 mg for three months are reported.

Subjects consisted of 12 women, among whom nine were treated for leiomyomas and four for endometriosis (one patient also had leiomyomas).

Based on examinations carried out, the biggest decrease of the uterus and leiomyomas was 13-17% observed just after two doses of analog, though after the end of treatment the dimensions of the uterus slowly increased. Therefore, 2-month therapy could be used successfully as preparation for further conservative surgical treatment.

Significant increase of body weight in treated patients was not observed. In women with endometriosis pain symptoms in the hypogastric area and dyspareunia regressed during treatment and at the end were not observed.

The disadvantages of therapy with Decapeptyl Depot 3.75 was the rapid occurrence of symptoms – climacteric signs, especially hot flashes – which were badly tolerated by patients. All these symptoms almost totally regressed one month after ending therapy.

Key words: a-GnRH; Uterine myoma; Endometriosis.

INTRODUCTION

When Schally's research ([1]) led to differentiation, identification and finally synthesis of GnRH, nobody expected that during the following years thousands of analogs of that neurohormone would be produced – analogs different from the endogenous one – with one or several aminoacids changed into decapeptide chains. Only some of them were introduced into therapy because of better affinity and longer effective half-time of duration (T½) than the natural GnRH. One of them is Tryptoreline, which is the active substance of Decapeptyl, and is synthetic and the closest analog to natural GnRH. The only difference is in changing L-Glycine with D-Tryptofane into position 6 in the chain.

Tryptoreline creating a firm binding witht GnRH receptors in the pituitary gland reduces the amount of receptors and diminishes the excretion of LH and FSH which leads to a decrease of 17-β estradiol excretion by the ovaries. This steroid is responsible for the growth of uterine leiomyomata in 20-30% of women aged

Received February 20, 1996 from the 2nd Dept. of Obstetrics & Gynecology, Medical University of Gdańsk, Poland

Revised manuscript accepted for publication April 29, 1996.

30 or more, and also endometriosis in 18% of women, of which 30-35% are infertile ([2, 3, 4, 5]).

The aim of this study was to estimate the efficiency of GnRH analog – Decapeptyl Depot – in treating uterine leiomyomata and endometriosis.

MATERIAL AND METHODS

The subjects consisted of 12 women ranging in age from 25 to 52 (mean 41.33 ± 8.51) qualified for therapy with GnRH analog. The indication for therapy with Decapeptyl Depot 3.75 mg (DD) in nine women was uterine leiomyomata. Qualification was made after gynaecological and USG examination. In four endometriosis was confirmed with histopathological diagnosis of biopsies taken in laparoscopy from Douglas case was indication, in one case concomitant with leiomyoma. All patients were referred for surgical treatment.

The DD therapy includede three doses of the drug, administered intramuscularly with 28 day intervals.

During the first hospitalisation between I and III day of the ovarian cycle the concentration of various hormones was examined: FSH, LH, PRL, E2, Progesterone, Testosterone, DHEA. In patients with diagnosed endometriosis the level of CA 125 was also checked. Women were examined gynaecologically and with an USG device B&K with a head type Convex (5 MHz) and an intravaginal one (7 MHz). The USG examination consisted of an estimation of uterine dimensions and the volume and localization of uterine leiomyomata. Three dimensions in two surfaces were estimated:

– longitudinal surface - length of uterine (from cervix to the bottom) and
– anterior-posterior dimension;
– horizontal surface - the width of the uterine.

After examination Decapeptyl Depot 3.75 mg was administered intramuscularly.

During two subsequent hospitalization apart from administration of II and III doses of the drugs, an extensive interview with patients about the side effects of therapy was made. The fourth hospitalization consisted only of an examination and interview without drug administration. The side effects were estimated based on a climacteric index according to Kupperman ([6]). Apart from that, attention was paid to time of occurrence and duration of bleeding, regression of dyspareunia and pain in the hypogastric area, a body weight was measured.

Follow up with 3 month intervals is being done after the last DD administration.

RESULTS

Twenty-eight days after first administration of DD body weight increased by 2 kg (mean), but stayed at that level for the next two months. At visits IV body weight loss was observed, mean of 2 kg below the initial value. The differences were not statistically significant (Table 1).

Mean levels of hormones examined and CA 125 are shown in Table 2.

The lowest level of FSH was observed 28 days after the first dose – 2.98 ± 1.34 IU/ml, of LH - 28 days after the second dose – it was below 1 IU/ml, and three months after the last dose the level of FSH significantly increased, and LH was higher than before the beginning of therapy.

The lowest levels of 17-β estradiol – below 30 pg/ml were observed after the second dose of DD. One month after the end of therapy the concentration of E2 reached 50 pg/ml, and the next two months reached a level almost twice as high as before therapy. The concentration of progesterone after a significant decrease

Table 1. — *Patient body weight during therapy with Decapeptyl Depot.*

	Before administering drug (1-3 days of the cycle) n. = 12	28 days after dose I, on the day of administering dose II	28 days after dose II, on the day of administering dose III	28 days after dose III
Average patient body weight ± SD (in kg)	63.64 ± 11.41	65.40 ± 12.92	65.91 ± 12.74	61.89 ± 0.70

after the first dose of DD showed no difference during follow-up, though the level was significantly lower than before therapy.

Testosterone levels were balanced and did not depend on the duration of treatment and amount of doses. The concentration of DHEA during treatment increased and after ending decreased by almost 50%.

In the group of patients with diagnosed endometriosis the level of CA 125 was also checked. A significant decrease of this marker was found in consequent examinations and it correlated with the regression of clinical symptoms (dyspareunia, pain in sacro-uterine ligaments) in this group.

After dose I of drug the dimensions of the uterus diminished (Table 3); the average length by 7.7%, anterior-posterior by 10.6%, transversal 6.16% and the diameter of the uterine leiomyomata by 7.91%. Twenty-eight days after dose II the uterus and leiomyomata consequently diminished by 12.58 %, 17.04 % and 12.8 %, respectively. But 28 days after dose III all dimensions of the uterus and leiomyomata diameters increased. The dimensions, however, of both the uterus and leiomyomata remained smaller than at the beginning of therapy.

A difference in amount of examinable leiomyomata during therapy was not found.

The frequency of the occurrence of side effects during DD therapy reported by patients is shown in Table 4. The most frequent, 75-100 %, were hot flushes. Ten patients (83%) after dose I reported bleeding (from spotting to full menses) of different durations (from 1 to 20 days). One patient felt depressed and needed psychiatric consultation. The majority of symptoms increased with the duration of therapy, but headaches, dyspareunia and bleeding regressed.

Table 2. — *Changes of mean concentrations of hormones and CA 125 (marker checked only in patients with diagnosed endometriosis).*

Hormone n. = 12	Before aministering drug (1-3 days of the cycle)	28 days after dose I, on the day of administering dose II	28 days after dose II, on the day of administering dose III	23 days after dose III	3 months after dose III
FSH (IU/ml)	7.25 ± 4.73	2.98 ± 1.34	3.05 ± 1.71	3.84 ± 1.71	6.32 ± 3.42
LH (IU/ml)	7.42 ± 7.99	1.25 ± 0.45	1	2.8 ± 5.35	9.0 ± 8.32
E2 (pg/ml)	69.58 ± 36.75	32.73 ± 13.68	28.42 ± 12.92	50.18 ± 68.16	129.67 ± 96.96
Progesterone (ng/ml)	0.73 ± 0.78	0.46 ± 0.27	0.44 ± 0.19	0.41 ± 0.23	0.41 ± 0.23
Testosterone (ng/100 ml)	42.42 ± 23.20	34.17 ± 15.74	46.83 ± 17.47	33.50 ± 16.21	48.67 ± 13.62
DHEA (ng/100 ml)	466.42 ± 357.62	540.92 ± 258.61	619.73 ± 423.22	285.60 ± 184.89	244.60 ± 184.99
PRL (µg/ml)	263.08 ± 271.61	150.00 ± 102.52	199.58 ± 265.08	264.60 ± 305.95	422.60 ± 291.32
CA 125 (IU/ml)	41.20 ± 16.90	10.00 ± 4.00	8.40 ± 1.82	8.33 ± 153	n = 4

Table 3. — *Average dimensions of the uterus and uterine leiomyomata during therapy with Decapeptyl Depot.*

Dimensions of the uterus	Before administering drug (1-3 d. c.) n. = 12	28 days after dose I		28 days after dose II		28 days after dose III	
	mm	mm	%*	mm	%*	mm	%*
Length in mm	95.58 ± 15.38	88.25 ± 12.81	7.67	83.55 ± 11.87	12.58	95.33 ± 17.72	0.26
Anterior-posterior dimension (p-t) w mm	56.58 ± 19.82	50.56 ± 16.82	10.64	46.73 ± 16.02	17.04	49.78 ± 10.60	12.01
Width in mm	67.67 ± 11.97	63.50 ± 12.91	6.16	57.64 ± 13.90	14.82	62.56 ± 22.50	7.55
Diameter of leiomyomata in mm	37.88 ± 18.60	34.88 ± 19.75	7.91	33.00 ± 20.42	12.88	36.60 ± 25.49	3.37

(*) Reduction of dimensions in percent according to examination before starting therapy.

DISCUSSION

Intramuscular administration of Decapeptyl Depot 3.75 mg for three months significantly influenced the diminishing not only of particular leiomyomata (by almost 13%) but all dimensions of the uterus by an average 12.5-17% as well. The results are comparable with results of other Authors independent of method and time – 3-6 months of analog admini-

Table 4. — *Frequency of occurrence of side effects during therapy with Decapeptyl Depot.*

Symptoms	28 days after dose I		28 days after dose II		28 days after dose III	
	%	n.	%	n.	%	n.
Hot flashes	75	9	92	11	100	12
Vertigo	8	1	33	4	33	4
Weakness	33	4	50	6	58	7
Depression	33	4	25	3	33	4
Palpitation	17	2	17	2	33	4
Headaches	42	5	25	3	17	2
Articulation aches	17	2	17	2	33	4
Memory disorders	17	2	42	5	50	6
Decrease of libido	17	2	50	6	67	8
Dysuria	0	0	8	1	8	1
Bleeding	83	10	25	3	17	2
Pain in hypogastric area	17	2	17	2	25	3
Dyspareunia	17	2	8	1	0	0

stration ([7, 8, 9, 10, 11, 12]). Further observations after ending therapy showed that the uterus and uterine leiomyomata increased, but it was not a rapid process.

Some of the patients did not come for further hormonal examinations, but all of them are under our constant surveillance and the uterine dimensions even four months after ending therapy are smaller than before administering DD. None of them have undergone surgery so far, but it is hard to say anything about future treatment.

A significant reduction of leiomyomata, the biggest after two doses of DD, allows us acknowledge that in women who want to maintain the uterus, the best moment for conservative myomectomy is two months after the start of treatment. Also the decision for uterine extirpation – in elderly women – should be taken into consideration after two months of preparation with DD.

The reduction of dimensions of the uterus and uterine leiomyomata improves surgical conditions and permits faster operations with less blood loss ([13]). Such pharmacological preparation may be of essential importance before extirpation via the vagina ([14]). According to van Lendsen ([15]) after 6 months treatment with DD the volume of the leiomyomatous uterus diminished by 31% and remains so. Thus, there is no need for surgical treatment.

The negative side of analog therapy are deficiency symptoms, characteristic of the climacteric period, which occurr suddenly and with great intensity. The hot flushes reported by all our patients were extremely trying. Other symptoms were not so frequent (Table 4). Other Authors have reported the same observations ([10, 15]).

Ninety-eight percent of the patients examined by Zorn ([16]) had hot flashes. Other symptoms like headaches and insomnia occurred in 50%. Body weight gain from 1-5 kg was noted in 34% of patients. In our subjects we observed a body weight gain of about 2 kg average. In four patients with endometriosis we noticed, despite all deficiency symptoms, an improvement in mood because of the total elimination of dyspareunia.

The pain in the hypogatric area regressed significantly in these patients.

After ending DD therapy the deficiency symptoms regressed, but dyspareunia and pain in the hypogastric area did not reappear.

Altering of the hormonal state during treatment with DD (Table 2) caused deficiency symptoms.

The most important determinant of the state of the patients was a decrease in levels of LH, FSH and E2. A decrease in 17-β eestradiol below 30 pg/ml was especially essential for positive effects in the treatment of endometriosis and uterine leiomyomata although some deficiency symptoms occurred (Table 4). Other Authors report similar observations ([10, 16, 17]).

Based on examinations carried out (though on a small number of patients) we may come to the subsequent conclusions.

CONCLUSIONS

1. Decapeptyl Depot 3.75 mg may be successfully administered to prepare patients with uterine leiomyomata for conservative myomectomy. The required period is two months (two injections).

2. Patients before the therapy should be psychologically prepared for sudden deficiency symptoms connected with blocking the pituitary gland and reducing levels of E2.

3. In monitoring the treatment of endometriosis marker CA 125 may be used. During treatment its value decreases with the regression of ailments connected with the disease.

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