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A crossover study of triptorelin and leuprorelin acetate

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Objective: To compare the potency, side effects, and duration of action of triptorelin and leuprorelin acetate after i.m. injections.

Design: Prospective, double-blind crossover clinical study.

Setting: A teaching hospital.

Patient(s): Fifty-four patients with pelvic endometriosis.

Intervention(s): Twenty-seven patients had three doses of i.m. triptorelin (3.75 mg) followed by three doses of i.m. leuprorelin acetate at 4-week intervals. Twenty-one patients had three doses of i.m. leuprorelin acetate (3.75 mg) followed by three doses of i.m. triptorelin, also at 4-week intervals.

Main Outcome Measure(s): Menopausal symptoms, time taken for menstruation to return, serum E_2, FSH, LH levels, lipid profiles, and liver function tests.

Result(s): The potencies of triptorelin and leuprorelin acetate in lowering the serum E_2, FSH, and LH levels were comparable. The severity of menopausal symptoms, changes in the lipid profile and liver function parameters were similar after triptorelin and leuprorelin acetate. The resurgence of ovarian activities and the spontaneous return of menstruation occurred significantly earlier after leuprorelin acetate than triptorelin.

Conclusion(s): Both drugs are equally potent in down-regulating the pituitary-ovarian function, and their side effects are similar. Triptorelin has a longer duration of drug action and can be administered over a longer interval period. (Fertil Steril® 2000;74:299–305. ©2000 by American Society for Reproductive Medicine.)

Key Words: Gonadotropin-releasing hormone agonists, GnRH-a, triptorelin, leuprolide acetate, endometriosis

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Endometriosis is estrogen dependent, and the condition improves in a low-estrogen milieu. This happens after natural menopause or bilateral oophorectomy. The serum estrogen level can also be reduced by medications, including progestogens (1–4), combined estrogen and progestogen (3), danazol (2, 5, 6), and gonadotropin-releasing hormone agonist (GnRH-a) (5, 7–11). Since the 1980s, GnRH-a has gained predominance because it is the most effective treatment in lowering the serum estrogen. As a result, patients receiving GnRH-a suffer mainly from menopausal symptoms and related changes.

Many GnRH-a formulations are available, and they differ from the native gonadotropin, which is a decapeptide, by one amino acid (aa) at the sixth position, and some also by another aa at the tenth position (12). The substitution of an aa at these positions is crucial because it increases the drug's resistance to peptidases, prolongs the drug's half-life, and increases its potency. The GnRH-a formulations are characterized by their unique modifications and are administered through different routes. Parenteral administration is usually preferred to nasal aerosols in the treatment of endometriosis, because drug compliance and drug bioavailability are more predictable. The three commonly used depot preparations, namely leuprolide acetate, triptorelin, and goserelin, are given as monthly injections and have been effective against endometriosis (7, 9, 11). Because the aa sequences of these three depot GnRH-a are different, it is possible that the potency, associated side effects, and duration of action are not the same.

Few clinical studies directly comparing these depot preparations have been performed. A randomized comparison between triptorelin

TABLE 1

Treatment and assessment schedule of the study.

Study period	Phase I						Phase II		
Follow up visits (wk)	0	4	8	12	16	20	24	28	32
Patient group									
T-L	Trp	Trp	Trp	Leu	Leu	Leu			
L-T	Leu	Leu	Leu	Trp	Trp	Trp			
Clinical assessment	Yes			Yes			Yes		
LH, FSH, E_2	Yes	Yes	Yes	Yes			Yes	Yes	Yes
LFT, lipid profile	Yes			Yes			Yes		

Note: T-L = the first three doses are triptorelin and the second three doses are leuprolide acetate; L-T = the first three doses are leuprolide acetate and the second three dose are triptorelin; Trp = triptorelin; Leu = leuprolin acetate; LFT = liver function test.

Cheung. Triptorelin and leuprorelin acetate study. Fertil Steril 2000.

and leuprorelin acetate has been conducted in patients with prostate cancer, and triptorelin has been shown to induce a greater decrease in testosterone than leuprorelin acetate (13). A study comparing the suppressive capacity of triptorelin, leuprorelin acetate, and goserelin given through i.m. showed that goserelin appeared to be less potent than the other two in suppressing the pituitary response to GnRH stimulation (14).

This study was designed to compare the potency, side effects, and the duration of drug action between leuprorelin acetate and triptorelin.

MATERIALS AND METHODS

Study Design

This study was approved by the Institutional Review Board of the Chinese University of Hong Kong. From August 1997 to June 1999, 54 patients diagnosed as having pelvic endometriosis after surgery and who had indications for GnRH-a therapy were recruited at the Prince of Wales Hospital, Hong Kong. All of them gave their written informed consent. Patients were advised to use nonhormonal forms of contraception after the recruitment and throughout the treatment period. Patients with endocrine disorders or receiving medication that could disturb the hypothalamo-pituitary-ovarian axis in the past 3 months were not recruited for the study.

The patients were randomly placed into two groups. The patients in the T-L group received 3.75 mg i.m. triptorelin (Decapeptyl; Ferring Pharmaceuticals Ltd., The Netherlands) once every 4 weeks for three doses, followed by 3.75 mg i.m. leuprorelin acetate (Enantone; Takeda IMC Ltd., Japan) once every 4 weeks for three doses. The time interval between the third dose of triptorelin and the first dose of leuprorelin acetate was also 4 weeks.

The patients in the L-T group received the same schedule of i.m. injections, but the first three doses of GnRH-a were leuprorelin acetate, whereas the second three doses were triptorelin. Both the patient and the assessors were unaware of the order of the drug sequence, and the first dose of GnRH-a was given within the first 7 days of menstruation (Table 1).

The study could be divided into two phases. The first study phase spanned from the commencement of treating with GnRH-a to 4 weeks after the first three doses were given. Hormonal and side effect profiles were compared after receiving one to three doses of GnRH-a between the two groups to determine the possible differences in drug potency. The second study phase spanned from 4 weeks after the completion of the second three doses of GnRH-a until the return of menstruation. The results obtained after the crossover were used to verify the earlier findings. Because there was no drug-free period between the switching from the first to the second GnRH-a, a comparison between the two groups was not conducted after the fourth and fifth doses of GnRH-a. In addition to the between-group comparisons, results obtained before and after the crossover in each group were compared where appropriate.

Clinical Assessment

Patients were evaluated before the commencement of treatment, and the subsequent assessment schedule is detailed in Table 1. Clinical assessment included: [1] menopausal symptoms; [2] the incidence and severity of vaginal bleeding in the immediate 4 weeks after each of the first three injections; and [3] the time taken for menstruation to return after the completion of GnRH-a.

Twelve menopausal symptoms (hot flushes and sweating, palpitation, anxiety, insomnia, depression, fatigue, headaches, paraesthesia, formication [a sensation as if small insects are creeping under the skin], arthalgia, vaginal dryness and irritation, and vertigo and dizziness) were assessed through interviews, and the severity of symptoms were categorized as none, slight, moderate, and marked. The worsening of individual symptoms was analyzed in the following manner. An increase in the severity over the baseline was regarded as positive, and no change or a reduction in the

degree of symptoms was regarded as negative. Furthermore, a Kupperman index was derived and was weighted in favor of hot flushes (multiplied by 4) and insomnia, anxiety, and arthalgia (multiplied by 2) in the same manner described in the previous report (15). A value of 0 was given for no experience of symptoms, 1 for slight, 2 for moderate, and 3 for severe. The maximum total score was 54, after weighting the symptoms.

Biochemical Assessment

Laboratory tests were used to determine the effects and side effects of the GnRH-a (Table 1). Serum E_2, LH, and FSH were measured to determine the effects of the drug on the pituitary-ovarian axis. Blood samples were collected before treatment, 4 weeks after the first injection, 4 weeks after the second and third injections, and three times after the sixth injection at 4-week intervals or until menstruation returned. No assessment was made after the fourth and fifth injections. Side effects of the GnRH-a were assessed by the serum level of triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoproteins A-I and B (apo A-I and apo B), lipoprotein (a) (Lp[a]), and a liver function test before the first dose and 4 weeks after the third and sixth injections.

After the administration of GnRH-a, serum levels of E_2 and LH might fall below the lowest level of discrimination. When this occurred to >10% of patients, the proportion of patients below the endometrial threshold level (150 pmol/L) or the lowest level of discrimination of LH (0.5 IU/L) were used for comparison. For the assessment of FSH suppression, the proportion of patients with serum levels of ±4 IU/L was used.

Hormone and Lipid Assays

Ten milliliters of clotted blood was collected from each subject as they returned for assessment, and the resulting serum was preserved in aliquots at −80°C until batch analysis.

Serum E_2, FSH, and LH were measured by a microparticle immunoassay (IMx analyzer; Abbott Laboratories, Abbott Park, IL) with interassay coefficients of variation (CV) of 6.5% at 1,835 pmol/L, 2.6% at 24.5 IU/L, and 4.5% at 40 IU/L, respectively. The lowest levels of discrimination for these three hormones were 90 pmol/L, 0.5 IU/L, and 1.0 IU/L, respectively.

Serum TC and TG were assayed enzymatically (Hitachi 911 analyzer; Boehringer Mannhein, Mannhein, Germany). The HDL-C was measured after precipitation of apo B containing lipoproteins with phosphotungstate. The LDL-C was calculated with use of the Friedewald Formula (16). Apo A-I and B and Lp (a) were assayed by rate immunonephelometry (Array analyzer and reagents, Beckman Instruments, Brea, CA). Interassay CVs were as follows: TC, <1.40% at 3.2 and 7.8 mmol/L; TG, 2.69% at 0.92 mmol/L; apo AI, 4.5% at 115 mg/dL, apo B, 4.9% at 103 mg/dL, and Lp(a), 3.9% at 28 mg/dL.

TABLE 2

Characteristics of the patients in the T-L and L-T groups.

Characteristics	Patient group	
	T-L (n = 27)	L-T (n = 21)
Age (y)	32.8 ± 1.4	35.8 ± 1.3
Weight (kg)	55.6 ± 1.5	59.1 ± 2.9
Body mass index (kg/m^2)	22.3 ± 0.6	24.8 ± 1.2
Cycle length (d)	29.1 ± 0.7	28.8 ± 0.6
Kuppermann index (weighted)	3.3 ± 0.9	4.0 ± 0.8
Pretreatment		
E_2 (pmol/L)	424.5 ± 67.4	500.7 ± 93.8
FSH (IU/L)	12.3 ± 1.8	8.6 ± 1.3
LH (IU/L)	9.2 ± 1.3	13.3 ± 4.5

Note: Values are means ± SEM.

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Statistical Analysis

Data are expressed as means ± SEM except for E_2, FSH, and LH. Patients' characteristics were compared by *t*-tests or Mann-Whitney tests whenever appropriate. Within-group changes in hormonal profiles were examined by McNemar's tests, whereas between-group changes were analyzed by Fisher's exact tests. Changes in lipid profiles and liver function test parameters from the compared baseline were examined by paired *t*-tests, and two-sample *t*-tests were used to compare whether these changes were statistically significantly different between groups. Any worsening of the menopausal symptoms was analyzed by the χ^2 test.

A two-tailed significance test was used for all comparisons, and $P<.05$ was considered statistically significant. Bonferroni's adjustment to the *P* value was applied where appropriate. The statistical analysis was performed with the use of SPSS for Windows (v 8.0) (SPSS Inc., Chicago, IL).

RESULTS

Fifty-four patients were recruited, and six were excluded from the analysis. Two patients refused to have GnRH-a after the randomization; one patient defaulted after the fourth injection and another after the sixth; one was diagnosed to have carcinoma of breast after the fourth injection and the GnRH-a treatment was terminated; and another was found to be pregnant after the fourth injection. In the final analysis, there were 27 patients in the T-L group and 21 patients in the L-T group. The patients' characteristics are summarised in Table 2. There was no statistically significant difference between the two groups before treatment in terms of age, weight, body mass index (BMI), cycle length, Kuppermann index, and serum levels of E_2, FSH, and LH.

Between-group and within-group comparisons of the hor-

TABLE 3

Hormonal profile after the GnRH-a treatment.

Patient group		4 weeks after 1st dose	4 weeks after 2nd dose	4 weeks after 3rd dose	4 weeks after 6th dose	8 weeks after 6th dose	12 weeks after 6th dose
T-L (n = 27)	E_2 (<150 pmol/L)	92.6	80.8	85.2	92.6	51.9[a]	29.6
	FSH (<4 IU/L)	73.1	61.5	53.9	27.0[b]	7.4	7.4
	LH (<0.5 IU/L)	40.7	84.6	88.9	81.5	29.6[c]	0.0[d]
L-T (n = 21)	E_2 (<150 pmol/L)	90.5	71.4	80.0	85.0	80.0	50.0
	FSH (<4 IU/L)	70.0	33.3	30.0	25.0	20.0	10.0
	LH (<0.5 IU/L)	57.1	85.7	95.0	95.0	100	60.0

Note: Values are percentages of patients; T-L group = the first three doses are triptorelin and the second three doses are leuprorelin acetate; L-T group = the first three doses are leuprorelin acetate and the second three doses are triptorelin.

[a] $P=.047$ vs. L-T group.

[b] $P<.02$ vs. 4 weeks after the third dose in the same group.

[c] $P<.01$ vs. L-T group.

[d] $P<.01$ vs. L-T group.

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monal profile were made after the GnRH-a administration (Table 3). No statistically significant differences in serum E_2, FSH, and LH levels was found between the two groups 4 weeks after the first, second, and third doses of triptorelin or leuprorelin acetate. Approximately 70%–90% of patients in both groups had E_2 below the endometrial threshold before and after the crossover. Within the L-T group, no differences in the E_2, FSH, and LH levels were noted 4 weeks after the three doses of leuprorelin acetate or 4 weeks after three doses of triptorelin. The same was also noted in the T-L group for the E_2 and LH levels but not the FSH level. The proportion of patients with FSH levels of >4 IU/L 4 weeks after the three doses of leuprorelin acetate (53.9%) and 4 weeks after the three doses of triptorelin (27.0%) was statistically significantly different ($P<.02$).

Changes of liver function test parameters and serum lipid profiles were studied 4 weeks after the third dose of GnRH-a (Table 4). No significant increase from the pretreatment level was noticed in any of the parameters after three doses of triptorelin in the T-L group. Four parameters, namely, total bilirubin, LDL-C, apo A-I, and apo B, showed a significant increase from the pretreatment level after three doses of leuprorelin acetate in the L-T group. However, all these increases did not exceed the normal ranges. By comparing the changes of individual parameters between the two groups, the increase in total bilirubin was significantly higher ($P=.025$) after three doses of leuprorelin acetate (3.00 ± 3.58 μmol/L) than after three doses of triptorelin (0.61 ± 2.08 μmol/L).

There was no statistically significant difference in the emergence of menopausal symptoms after the first three doses of GnRH-a in either group. The increase in the Kuppermann index in both groups was also comparable at that juncture (Table 5). The difference in the percentage of patients with significant vaginal bleeding, defined as requiring more than two pads per day, in the first 4 weeks after the first dose of triptorelin (33.3%) or leuprorelin acetate (42.9%) was not significant. More than 90% of patients in both groups remained amenorrhoeic after the second or third dose of triptorelin or leuprorelin acetate, and the difference was insignificant.

Serum E_2, FSH, LH, and the time taken for the menstruation to return were used to assess the resurgence of ovarian activity. Eight weeks after the last dose of GnRH-a, more patients in the L/T group (80.0%) than T-L group (51.9%) had serum E_2 levels below the endometrial threshold. The difference was statistically significant ($P=.047$). The corresponding percentages remained higher in the T-L group (50.0%) than the L-T group (29.6%) at 12 weeks, but the difference was insignificant (Table 3). Eight weeks after receiving the last dose of leuprorelin acetate in the T-L group and triptorelin in the L-T group, a statistically significant difference ($P<.01$) in the percentage of patients showing LH of <0.5 IU/L was noted between the T-L group (30%) and the L-T group (100%). This difference remained ($P<.01$) between the groups 12 weeks after the last dose of leuprorelin acetate (0%) or triptorelin (60%). The FSH levels between the two groups were comparable 8 and 12 weeks after the last dose of leuprorelin acetate or triptorelin.

The time taken for the menstruation to return was significantly longer ($P=.002$) after the last dose of triptorelin in the L-T group (129.2 ± 6.8 days) than after the last dose of leuprorelin acetate in the T-L group (103.6 ± 4.5 days).

DISCUSSION

Triptorelin differs from native gonadotropin by one aa at the sixth position, whereas, leuprorelin acetate substitutes

TABLE 4

Lipid profile and liver function test parameters before and after three doses of GnRH agonist.

Patient group	Parameters	Baseline	Week 12	Value change	*P* value
T-L (n = 27)	T Bil (μmol/L)	6.65 (0.53)	7.26 (0.61)	0.61 (0.43)[a]	NS
	ALP (IU/L)	58.78 (3.48)	65.70 (3.91)	6.91 (2.43)	NS
	SGPT (IU/L)	22.96 (2.21)	27.09 (2.97)	4.13 (2.65)	NS
	Cholesterol (mmol/L)	5.06 (0.15)	5.28 (0.16)	0.22 (0.12)	NS
	Triglyceride (mmol/L)	1.08 (0.13)	1.00 (0.10)	−0.08 (0.10)	NS
	HDL-C (mmol/L)	1.44 (0.08)	1.53 (0.07)	0.09 (0.08)	NS
	LDL-C (mmol/L)	3.12 (0.14)	3.29 (0.14)	0.17 (0.11)	NS
	Apo A-I (mg/dL)	143.43 (4.97)	155.70 (3.71)	12.27 (4.40)	NS
	Apo B (mg/dL)	83.30 (4.90)	84.07 (4.32)	0.76 (2.79)	NS
	Lp(a) (mg/dL)	19.62 (2.98)	21.31 (3.09)	1.69 (1.59)	NS
L-T (n = 21)	T Bil (μmol/L)	5.63 (0.67)	8.63 (1.17)	3.00 (0.90)	0.004[b]
	ALP (IU/L)	61.00 (3.13)	67.25 (6.61)	6.25 (4.92)	NS
	SGPT (IU/L)	21.69 (2.45)	31.98 (5.46)	10.29 (4.64)	NS
	Cholesterol (mmol/L)	5.13 (0.21)	5.53 (0.22)	0.40 (0.13)	NS
	Triglyceride (mmol/L)	1.74 (0.26)	1.65 (0.31)	−0.09 (0.14)	NS
	HDL-C (mmol/L)	1.19 (0.07)	1.24 (0.08)	0.04 (0.04)	NS
	LDL-C (mmol/L)	3.14 (0.19)	3.54 (0.19)	0.40 (0.12)	0.03[b]
	Apo A-I (mg/dL)	135.67 (4.02)	143.76 (4.38)	8.10 (2.33)	0.02[b]
	Apo B (mg/dL)	88.89 (5.13)	97.61 (5.43)	8.72 (2.71)	0.04[b]
	Lp(a) (mg/dL)	21.63 (5.40)	24.27 (5.22)	2.64 (1.98)	NS

Note: Values are means ± SEM; NS = not significant; T-L group = received three doses of triptorelin; L-T group = received three doses of leuprorelin acetate; T Bil = total bilirubin; ALP = alkaline phosphatase; SGPT = serum glutamic-pyruvic transaminase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Apo-A-I = apolipoproteins A-I; Apo B = apolipoproteins B; Lp(a) = Lipoprotein (a).

[a] Significant difference in the change between the T-L and L-T groups.

[b] Significant change from baseline in L-T group after three doses of leuprorelin acetate.

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amino acids at the sixth and tenth positions. The aa substitutions increase the drug's resistance to metabolism, prolong its action, and increase its potency. Although triptorelin and leuprorelin acetate are different biochemically, they are regarded as identical and are usually given i.m. at 4-week intervals to patients with endometriosis.

Identifying the possible differences in the duration of the drug's action between these GnRH-a is important. This allows a longer acting depot GnRH-a to be administered at longer intervals, to reduce both the cost and inconvenience to patients. It remains to be determined whether longer acting GnRH-a is associated with greater drug potency. Although a low-estradiol milieu is beneficial to the regression of endometriosis, extreme pituitary down-regulation by potent GnRH-a does not confer treatment benefits but does increase side effects.

Knowing the inhibition of pituitary-ovarian functions by nafarelin was dose dependent (8); 400 μg and 800 μg of nafarelin per day was given to patients with pelvic endometriosis, resulting in comparable improvements on the American Fertility Society score and the proportion of women with pain relief. Ten percent of patients in the high-dose group and none in the low-dose group withdrew from the study because of hot flashes (5).

A randomized study comparing intranasal nafarelin to i.m. leuprorelin acetate showed that leuprorelin acetate tended to have a stronger estrogen suppression, causing more vasomotor symptoms and bone loss without achieving any difference in the improvement of symptoms and signs

TABLE 5

Patients with worsening of menopausal symptoms 4 weeks after the third doses of GnRH-a.

	Patient group	
	T-L (n = 27)	L-T (n = 21)
Hot flushes and sweating	63.0	66.7
Paraesthesia	22.2	38.1
Insomnia	37.0	38.1
Anxiety	37.0	28.6
Depression	22.2	19.0
Vertigo and dizziness	18.5	9.5
Fatigue	29.6	28.6
Arthalgia	51.9	23.8
Headache	25.9	23.8
Palpitation	25.9	28.6
Formication	18.5	19.0
Vaginal dryness and irritation	22.2	14.3

Note: Values are percentages of patients.

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of endometriosis (7). A correlation between the climacteric symptoms and low serum estradiol has been shown in women between the ages of 35 and 39 (17). Therefore, evaluating the potency and side effect profiles of different depot GnRH-a is important.

Each patient recruited into this study received both triptorelin and leuprorelin acetate. A drug-free period was not inserted after finishing the three doses of the first GnRH-a before the crossover, or the treatment duration would have had to be prolonged. Therefore, the data collection and comparisons between the two groups after the fourth and fifth doses of GnRH-a were omitted. Because the recommended treatment interval is 4 weeks for triptorelin and leuprorelin acetate after i.m., we did not expect significant drug activity exceeding 8 weeks. We envisaged that any residual effects of the first three doses of GnRH-a to be minimal by the time the sixth dose of GnRH-a is given. A comparison between the two groups after the crossover, therefore, would be valid.

The research project could be divided into two study phases demarcated by the time of crossover. The first study phase spanned from the commencement of GnRH-a to 4 weeks after the first three doses of GnRH-a given. Hormonal and side effect profiles of the two groups were compared after receiving one to three doses of GnRH-a, and no difference was noted. The second study phase spanned from 4 weeks after the last dose of GnRH-a until the return of menstruation. Again, no difference could be found after the crossover.

These findings were consistent with an earlier study that showed the response of the pituitary gland to GnRH-a stimulation among women with normal menstruation was equally suppressed after three doses of triptorelin or leuprorelin acetate given i.m. (14). This suggested that triptorelin and leuprorelin acetate are equipotent in down-regulating the pituitary-ovarian function among female patients. This differs from the experience among patients with prostate cancer where triptorelin induced a greater decrease in testosterone levels than leuprorelin acetate (13). Whether a difference in potency between triptorelin and leuprorelin acetate consistently occurs in male patients remains to be confirmed.

Because $>$50% of the patients saw their serum E_2 levels fall below the lowest discriminatory level of our test, the absolute level could not be ascertained, and our comparisons were based on the proportion of patients with serum E_2 of $<$150 pmol/L, a level below which the endometrial tissue would become atrophic according to the estrogen threshold hypothesis (18). This cutoff, therefore, represents an indicator for drug efficacy in the treatment of endometriosis. A true difference between the triptorelin and leuprorelin acetate in lowering E_2 could be missed with this approach. However, the difference, if it exists, might well not be a major one, or clinically important. This notion was suggested by finding comparable clinical and biochemical side effects in the two groups after their first three doses of GnRH-a. Of the menopausal symptoms and lipid profile and liver function test parameters studied, the only significant differences noted between the two groups was the total bilirubin level. Because we used $>$20 parameters in looking for differences in side effects, a significant increase in TB level after three doses of leuprorelin acetate was thought to be incidental.

After receiving triptorelin injections, serum FSH levels increased sharply in the first 10 minutes and then declined to a low level by day 14. The FSH levels increased modestly throughout the triptorelin treatment period (9). In the T-L group, such an increase was more marked than in the L-T group, throughout the 6-month GnRH-a treatment period. As a result, the percentage of patients with FSH levels of $>$4 IU/L was significantly higher ($P=.016$) 4 weeks after three doses of leuprorelin acetate (73.1%) than after three doses of triptorelin (46.2%) in the T-L group. No such difference was noted in the L-T group where the triptorelin and leuprorelin acetate were given in a reverse order. The results suggest that the suppression of FSH was less effective after leuprorelin acetate than triptorelin.

The incidences and severity of side effects worsened with time. The mean weighted Kuppermann score in the T-L and L-T groups were 11.0 ± 7.6 and 10.0 ± 7.2, respectively, after the first three doses. These became 14.1 ± 7.6 and 15.8 ± 10.3 after the sixth dose of GnRH-a. Similarly, the lipid profile worsened as the treatment was prolonged. The significant time-period effect renders the within-group comparison of side effects inappropriate.

The duration of the drug actions of triptorelin and leuprorelin acetate was studied by documenting the resurgence of pituitary-ovarian functions clinically and biochemically. Eight weeks after the last dose of GnRH-a, a significantly ($P=.047$) lower percentage of patients in the T-L group treated with leuprorelin acetate (51.9%) compared to patients in the L-T group treated with triptorelin (80.0%) had serum E_2 levels remaining below the endometrial threshold. The difference disappeared at 12 weeks as the suppressive action of triptorelin had weakened by that time. The LH level was significantly higher in the T-L group than in the L-T group at 8 and 12 weeks after the last dose of GnRH-a. These represented an earlier recovery of the pituitary function after leuprorelin acetate. A significantly longer delay in the return of menstruation among patients in the L-T group than in T-L group further suggested that the resumption of the ovarian function occurred later after triptorelin.

The time taken for menstruation to return was 129.2 ± 6.8 days after the last dose of triptorelin in the L-T group. This is much longer than the findings in an early report where the spontaneous return of menstruation occurred 67 ± 2 days after the last dose of i.m. triptorelin (9). The body weight and body mass index of patients in that study did not differ significantly from those of our patients. Whether

the difference was attributable to ethnic origins remains to be determined.

Although we have shown that the duration of the action of triptorelin is longer than that of leuprorelin acetate, this study was unable to tell whether the prolongation of the drug's action was due to a difference in the aa sequence or the depot base. In conclusion, triptorelin remains active longer, and there is no difference in the potency and side effects of triptorelin and leuprorelin acetate.

References

1. Luciano AA, Turksoy RN, Carleo J. Evaluation of oral medroxyprogesterone acetate in the treatment of endometriosis. Obstet Gynecol 1988;72:323–7.
2. Vercellini P, Giorgi OD, Oldani S, Cortesi I, Panazza S, Crosignani PG. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis. Am J Obstet Gynecol 1996;175: 396–401.
3. Moghissi KS. Treatment of endometriosis with estrogen-progestin combination and progestogens alone. Clin Obstet Gynecol 1988;31:823–8.
4. Kaunitz AM. Long-acting injectable contraception with depot medroxyprogesterone acetate. Am J Obstet Gynecol 1994;170:1543–9.
5. Henzl MR, Corson SL, Moghissi K, Buttram VC, Berqvist C, Nafarelin Study Group. Administration of nasal nafarelin as compared with oral danazol for endometriosis. A multicenter double-blind comparative clinical trial. N Engl J Med 1988;318:485–9.
6. Meldrum DR, Pardridge WM, Karow WG, Rivier J, Vale W, Judd HL. Hormonal effects of danazol and medical oophorectomy in endometriosis. Obstet Gynecol 1983;62:480–5.
7. Agarwal SK, Hamrang C, Henzl MR, Judd HL, Nafarelin Study Group. Nafarelin vs. leuprolide acetate depot for endometriosis: changes in bone mineral density and vasomotor symptoms. J Reprod Med 1997; 42:413–23.
8. Monroe SE, Blumenfeld Z, Andreyko JL, Schriock E, Henzl MR, Jaffe RB. Dose-dependent inhibition of pituitary-ovarian function during administration of a gonadotropin-releasing hormone agonistic analog (nafarelin). J Clin Endocrinol Metab 1986;63:1334–41.
9. Filicori M, Cognigni GE, Arnone R, Pocognoli P, Tabarelli C, Ciampaglia W, et al. Subcutaneous administration of a depot gonadotropin-releasing hormone agonist induces profound reproductive axis suppression in women. Fertil Steril 1998;69:443–9.
10. Dlugi AM, Miller JD, Knittle J, Lupron Study Group. Lupron depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: a randomized, placebo-controlled, double-blind study. Fertil Steril 1990;54:419–27.
11. Venturini PL, Anserini P, Fasce V, Cucuccio S, Costantini S, Cecco LD. Treatment of endometriosis with goserelin depot, a long-acting gonadotropin-releasing hormone agonist analog: endocrine and clinical results. Fertil Steril 1990;54:1021–7.
12. Agarwal SK. Comparative effect of GnRH agonist therapy: review of clinical studies and their implications. J Reprod Med 1998;43:293–8.
13. Kuhn JM, Abourachid H, Brucher P, Doutres JC, Fretin J, Jaupitre A. A randomized comparison of the clinical and hormonal effects of two GnRH agonists in patients with prostate cancer. Eur Urol 1997;32:397–403.
14. Filicori M, Flamigni C, Cognigni G, Dellai P, Arnone R, Falbo A. Comparison of the suppressive capacity of different depot gonadotropin-releasing hormone analogs in women. J Clin Endocrinol Metab 1993;77:130–3.
15. Chung TK, Yip SK, Lam P, Chang AM, Haines CJ. A randomized, double-blind, placebo-controlled, crossover study on the effect of oral oestradiol on acute menopausal symptoms. Maturitas 1996;15:115–23.
16. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of LDL cholesterol in plasma without use of the preparation ultracentrifuge. Clin Chem 1972;18:499–502.
17. Abe T, Furuhashi N, Yamaya Y, Wada Y, Hoshiai A, Suzuki M. Correlation between climacteric symptoms and serum levels of estradiol, progesterone, follicle-stimulating hormone, and luteinizing hormone. Am J Obstet Gynecol 1977;129:65–7.
18. Barbieri RL. Endometriosis and the estrogen threshold theory: relation to surgical and medical treatment. J Reprod Med 1998;43:287–92.