Depot leuprolide acetate versus danazol in the treatment of women with symptomatic endometriosis: A multicenter, double-blind randomized clinical trial

II. Assessment of safety

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OBJECTIVES: This is the first multicenter, double-blind randomized clinical trial that compares a depot gonadotropin-releasing hormone agonist with danazol in the treatment of endometriosis. Efficacy results have been previously reported; this report focuses on safety data.

STUDY DESIGN: A total of 270 patients from 22 centers were randomly selected to receive either leuprolide acetate depot (3.75 mg injected monthly) or danazol (800 mg administered orally daily). Safety outcomes included adverse effects, clinical laboratory changes, and bone mineral density changes.

RESULTS: Most patients receiving either drug reported side effects, most of which were related to the hypoestrogenism of leuprolide (e.g., vasodilatation) and relative hyperandrogenism of danazol (e.g., weight gain). Similarly small numbers of patients dropped out of the two treatment groups because of the side effects encountered. Leuprolide depot caused a greater decrease in bone density; preliminary data suggest a return to baseline on cessation of the drug. Danazol was associated with alteration of serum lipids, specifically a significant decrease in high-density lipoprotein.

CONCLUSIONS: Although side effects were commonly reported in both groups, the drugs were similarly safe in terms of the absence of serious complications and the results of cessation of therapy. Side effects were largely reversible on discontinuation of medication. More longitudinal data are necessary before the possibility of long-term risks can be excluded, especially as they pertain to bone mineral density and lipids. (Am J Obstet Gynecol 1993;169:26-33.)

Key words: Endometriosis, gonadotropin-releasing hormone agonist, depot, danazol, randomized clinical trial

Endometriosis occurs in approximately 10% of all women of reproductive age and is a common cause of pelvic pain and of infertility.[1] The results of current medical and surgical therapy are disappointing because of high recurrence rates within a few years of treatment.[2, 3] In recent years medical therapy has favored the gonadotropin-releasing hormone (GnRH) agonists, which result in hypoestrogenism and then in atrophy of uterine and ectopic endometrial tissue.[4] Also, GnRH agonist side effects are related to the induced hypoestrogenic state, including hot flushes, insomnia, irritability, and bone loss.[1] In the United States GnRH agonist administration has required daily injections or inhalations; patient compliance may decline with the requirement of such frequent dosing over months of treatment. A depot form of GnRH agonist (leuprolide acetate for depot suspension, or Lupron Depot) provides continuous drug release for 4 weeks after intramuscular injection. A depot GnRH agonist may be more acceptable to women with endometriosis and therefore may increase the likelihood of their compliance. It can also offer potentially faster, more profound suppression of ovarian estradiol production. Our randomized clinical trial was conducted to compare the safety and efficacy of leuprolide acetate depot with that of standard danazol therapy in the treatment of women with symptomatic endometriosis. We have previously

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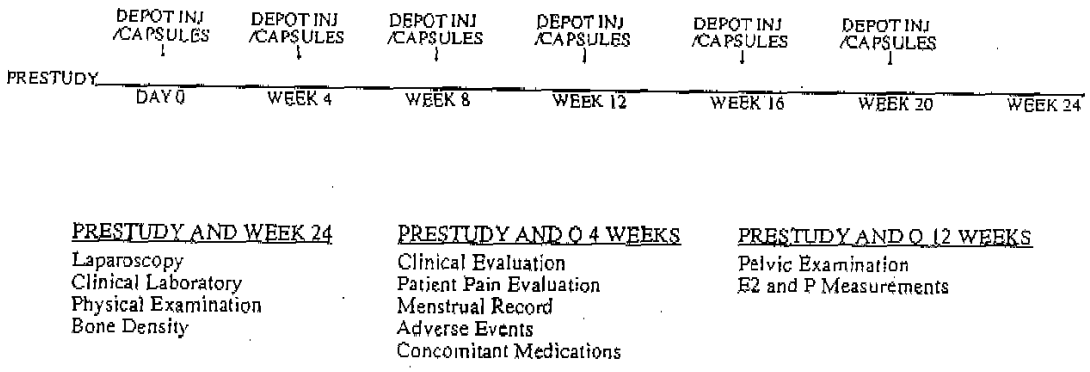

Fig. 1. Protocol summary of randomized clinical trial comparing leuprolide acetate depot versus danazol in treatment of women with symptomatic endometriosis. *E2*, Estrogen; *P*, progesterone.

reported efficacy results[5]; this article reports the safety of leuprolide acetate depot as compared with danazol.

Material and methods

Study design and medication. The details of this randomized clinical trial are described in the article wherein we reported on efficacy results.[5] To summarize, the study was a double-blind, multicenter randomized clinical trial between patients with symptomatic endometriosis treated for 24 weeks with either a monthly injection of 3.75 mg of leuprolide acetate depot or 800 mg daily oral administration of danazol. Pretreatment evaluation included general medical and endometriosis history, physical examination, laparoscopy with staging according to the Revised American Fertility Society classification,[6] and clinical evaluation of endometriosis signs and symptoms. Outcomes measured included patients' self-reports of pelvic pain and analgesic use, clinician grading of signs and symptoms,[7] and clinician grading of analgesic use.[8] Blood tests included routine complete blood cell count, serum chemistry studies, and pregnancy test; serum estradiol and progesterone levels were determined during both the follicular and luteal phases.

Each investigator determined bone density by his or her usual method. Bone mineral density of the spine was measured by dual-photon absorptiometry (DP3 Lunar Radiation, Madison, Wis.) in 17 centers and by quantitative computerized tomography (General Electric 9800, Milwaukee, or Siemens QCT, Madison, Wis.) in five centers. Bone mineral density of the femoral neck was measured by dual-photon absorptiometry in nine centers. Midshaft or distal radial density was measured by single-photon absorptiometry (SP2 Lunar Radiation, Madison, Wis.) at nine centers. Bone mineral density of the calcaneus was measured by single-photon absorptiometry at one center. All scan data were analyzed by a single investigator (J.C.G.) who was blinded to the treatment code. Bone mineral density values were expressed as percent change from baseline. Although each investigator standardized the measurement of bone mineral density of his or her patients, the varying methods and sites of measurement imparted an inherent degree of variation estimated at ±2% to 5%.[9, 10] Our trial sought to determine densitometry changes during actual clinical use of these drugs, so each investigator used his or her own standardized method; no attempt was made to standardize measurements between centers.

Subsequent monthly visits were standardized between the two study groups to maintain double blinding. At each visit patients were asked to describe any side effects possibly related to the prescribed medications. Laboratory tests related to safety included blood chemistry and hematology determinations and bone densitometry, all of which were performed at baseline and at week 24. Study protocol and procedures are depicted schematically in Fig. 1.

Patient selection. Case definition required laparoscopic diagnosis of endometriosis within 4 months of study entry; no surgical treatment of endometriosis or adhesions was permitted at the time of laparoscopy. Patients previously treated by any GnRH agonist were excluded. Any other treatment must have been completed > 3 months before study enrollment, and diagnostic laparoscopy must have been performed after discontinuation of previous therapy. Similarly, all patients who had previously taken oral contraceptives must have resumed normal spontaneous menses for at least two cycles before their enrollment in the study.

All patients who wanted to become pregnant underwent a thorough infertility evaluation. Each of the participating investigators is experienced in such evaluations; both the patients and their male partners were evaluated preoperatively. Barrier contraception was used throughout the study and for 6 weeks after the last depot injection.

All patients were premenopausal, nonpregnant, non-

lactating, and at least 18 years old. Women with baseline bone densitometry of >2 SD below the mean were excluded.

Statistical analysis. Sample size was calculated on the basis of the anticipated change in the Revised American Fertility Society's classification score.[6] This arithmetic classification has four categories of severity, with the least severe being "minimal disease" (1 to 5 points). Sample size was calculated to have an 80% statistical power to detect a 4-point difference between the two groups' mean score changes. With $\alpha = 0.05$, each study group was to contain 125 evaluable subjects for a total sample size of 250. Because all investigators entered patients in the study simultaneously, the projected goal of 250 patients was exceeded in the conduct of the trial.

Data were doubly entered and checked for accuracy. All data were depicted descriptively before inferential statistics were applied. Categoric data were compared by means of Fisher's exact or χ^2 tests with significance accepted at $p \leq 0.05$. Continuous data were compared with the use of t tests for independent samples. The Bonferroni correction for multiple tests was applied; significance was therefore accepted at $p \leq 0.001$. All tests were two-tailed.

Results

A total of 270 patients were enrolled by 22 U.S. investigators between Oct. 14, 1986, and Dec. 21, 1988. All 270 women enrolled were included in the evaluation of safety; 134 were randomly assigned to the leuprolide acetate depot group and 136 to the danazol group.

Assessment of efficacy. Both danazol and leuprolide acetate depot proved efficacious in treatment of the symptoms, signs, and laparoscopic findings in patients with symptomatic endometriosis. These results, as well as the hormonal data associated with treatment, have been previously presented.[5] Our present report focuses on assessment of safety.

Assessment of safety

Vital signs. The patients' ages ranged from 18 to 44 years, with no difference in mean age between the leuprolide and danazol groups (30.8 vs 29.9 years, $p_t = 0.09$).

There was no difference between the leuprolide depot and danazol groups in terms of mean height (64.9 vs 64.6 inches, $p = 0.33$) or weight (135.4 vs 134.3 pounds, $p = 0.72$) at baseline. Mean body weight after treatment increased significantly more in the danazol group than in the leuprolide depot group (5.0 ± 0.6 vs 2.0 ± 0.6 pounds, $p < 0.001$).

There were no significant differences at baseline between the leuprolide depot and danazol groups in systolic blood pressure (113.0 ± 1.0 vs 112.1 ± 1.0 mm Hg; $p = 0.55$), diastolic blood pressure (72.2 ± 0.8 vs 71.4 ± 0.8 mm Hg; $p = 0.52$), or pulse rate (75.0 ± 0.7 vs 75.3 ± 0.7 beats/min; $p = 0.74$). There were no significant changes in blood pressure or pulse between groups or within groups. No patient had hypertension during the trial; one patient in the leuprolide depot group had tachycardia (pulse rate >120 beats/min) that did not require further treatment.

Bone mineral density. In all categories of bone density measurement, the leuprolide group had greater mean loss of bone density than the danazol group (Table I); these changes reached statistical significance between the leuprolide and danazol groups for dual-photon absorptiometry and quantitative computerized tomography measurement of the spine and for single-photon absorptiometry measurement of the calcaneus. Of 87 leuprolide patients in whom dual-photon absorptiometry showed a decrease in spine density, 16 were followed up for an additional year after treatment; their net mean decrease improved to −2.57%. Of eight patients in the leuprolide group in whom quantitative computerized tomography showed decreased spine density, seven were followed up for an additional year, and their net mean loss improved to −0.89%.[11] These preliminary data suggest the return of GnRH agonist–related bone loss over time after treatment, but the data need to be strengthened by greater numbers and follow-up over longer periods of time.

Clinical laboratory determinations. Of the total of 270 patients enrolled, complete laboratory data are evaluable for 230 patients (118 in the leuprolide group, 112 in the danazol group). There were no baseline mean differences between groups in any of the clinical laboratory test results obtained. Laboratory data results are divided into hematology and coagulation factors (Table II), lipids (Table III), and serum chemistry values (Table IV). In each of these tables data are grouped according to the normal range, and changes after treatment are related to the normal range. It is hoped that relating the data in this categoric fashion is more clinically relevant than relating differences in mean values derived from so many individuals. Thus results are presented for the entire group, but emphasis is on those laboratory values that moved into or out of the normal range.

Table II shows that the majority (72% to 94%) of patients in both groups had no change in their pretreatment and posttreatment hematologic and clotting parameters. The only parameter with an overall significant difference across all categories by cross-tabulation analysis was partial thromboplastin time, with greater shortening of partial thromboplastin time in the danazol group than in the leuprolide depot group ($p < 0.001$). Between categories of patients, some significant differences were demonstrated by Fisher's exact tests. Patients in the danazol group were more likely to have an increase in their levels of hemoglobin ($p = 0.008$) or hematocrit ($p = 0.005$) than patients in

Table I. Bone mineral density measurement at baseline and percent change after treatment

Site	Method	Leuprolide acetate depot			Danazol		
		No.	*Baseline*	*Change (%)*	*No.*	*Baseline*	*Change (%)*
Spine	DPA (gm/cm^2)	102	1.230 ± 0.019*	−4.3 ± 0.4†	91	1.219 ± 0.020	−0.1 ± 0.5†
Spine	QCT (gm/cm^3)	8	177.3 ± 10.1	−15.1 ± 1.7‡	9	161.7 ± 9.5	+6.2 ± 1.7‡
Calcaneus	SPA (gm/cm^2)	20	0.401 ± 0.015	−2.8 ± 2.7§	20	0.394 ± 0.015	+1.6 ± 2.5§
Femoral neck	DPA (gm/cm^2)	38	0.950 ± 0.025	−2.7 ± 1.2	32	0.963 ± 0.027	−0.4 ± 1.3
Radius	SPA (gm/cm^2)	31	0.662 ± 0.018	−0.2 ± 2.0	30	0.648 ± 0.022	+1.2 ± 2.0

For all values without symbols, comparisons between drugs were not significant. *DPA*, Dual-photon absorptiometry; *QCT*, quantitative computerized tomography; *SPA*, single-photon absorptiometry.

*Amounts are mean ± SEM.

†$p < 0.001$.

‡$p < 0.001$.

§$p < 0.001$.

Table II. Effects of tratment with leuprolide acetate depot versus danazol on hematology and clotting factors

Factor and normal range	Drug	*No.*	*No change from baseline*		*Posttreatment change from baseline*				*Significance**
					Increase		*Decrease*		
			No.	*%*	*Low to normal*	*Normal to high*	*Normal to low*	*High to normal*	
Hemoglobin (12.0-16.0 gm/dl)	Leuprolide acetate depot	118	100	85	10	1	7	0	$p = 0.008$
	Danazol	112	95	85	10	7	0	0	
Hematocrit (37.0%-47.0%)	Leuprolide acetate depot	117	94	80	16	0	7	0	$p = 0.005$
	Danazol	110	76	69	21	12	1	0	
Platelet count (150-400,000/μl)	Leuprolide acetate depot	86	81	94	0	2	0	3	$p = 0.02$
	Danazol	77	59	77	1	16	0	1	
White blood cell count (4.5-11,000/μl)	Leuprolide acetate depot	115	101	88	2	3	6	3	NS
	Danazol	111	95	86	4	5	6	1	
Prothrombin time (10.8-12.8 sec)	Leuprolide acetate depot	113	102	90	0	1	5	5	NS
	Danazol	97	87	90	0	5	2	3	
Partial thromboplastin time (25-37 sec)	Leuprolide acetate depot	109	101	93	1	2	2	3	$p = 0.023$
	Danazol	93	67	72	1	0	23	2†	

NS, Not significant.

*Fisher's exact test of increase versus decrease per laboratory value.

†χ^2 cross tabulation, change across all categories; $p = 0.00004$. All other cross tabulations across categories according to laboratory value, not significant.

the leuprolide depot group. Among women with low to normal values, significantly more women with low levels of hemoglobin ($p = 0.026$) and hematocrit ($p = 0.046$) had a return of values to the normal range with danazol than with leuprolide depot. Patients in the danazol group were also more likely to have their platelet counts raised above the average range ($p = 0.02$). Patients in the danazol group were more likely to have their partial thromboplastin times shortened ($p = 0.023$) but not their prothrombin times ($p = 0.064$).

Table III shows that most patients had no change related to the normal range in their lipid values. However, cross-tabulation analysis demonstrated overall significance in changes between danazol and leuprolide acetate for high-density lipoprotein ($p = 0.000002$) and low-density lipoprotein ($p = 0.006$). For changes between categories by Fisher's exact tests, danazol was significantly more likely to lower high-density lipoprotein ($p = 0.0000009$)—in many cases below the normal range ($n = 47$). Although danazol was often associated with a rise of low-density lipoprotein above the normal range ($n = 19$), statistical significance ($p = 0.7$) between categories was not reached.

In Table IV focus is on those patients whose serum chemistry values were initially normal and then exceeded the normal range after treatment. Again, in

Table III. Effects of treatment with leuprolide acetate depot versus danazol on serum lipids

Factor and normal range	Drug	No.	No change from baseline		Posttreatment change from baseline				Significance
					Increased		Decreased		
			No.	%	Low to normal	Normal to high	Normal to low	High to normal	
Total cholesterol (120-240 mg/dl)	Leuprolide acetate depot	118	107	91	3	7	1	0	NS
	Danazol	108	93	87	3	9	3	0	
High-density lipoprotein (30-95 mg/dl)	Leuprolide acetate depot	107	96	90	3	4	2	2*	$p < 0.0001$
	Danazol	90	41	44	0	0	47	2	
Low-density lipoprotein (60-160 mg/dl)	Leuprolide acetate depot	98	85	87	4	5	3	1†	$p = 0.006$
	Danazol	88	61	69	2	19	2	4	

NS, Not significant.

*χ^2 cross tabulation across all categories, $p = 0.000002$; Fisher's exact test for increased versus decreased values, $p = 0.0000009$.

†χ^2 cross tabulation across all categories, $p = 0.006$; Fisher's exact test for increased versus decreased values, $p = 0.7$ (not significant).

most patients (82% to 96%) values stayed within the normal range; however, patients in the danazol group were more likely to have elevated levels of serum glutamic-oxaloacetic transaminase than patients in the leuprolide depot group ($p = 0.028$). No chemistry value of any patient increased to a level sufficient to require discontinuance of either drug.

Adverse effects. Adverse events were reported by 126 (94%) of the 134 patients in the leuprolide depot group and 122 (90%) of the 136 patients in the danazol group. Hot flushes were the most common adverse event and occurred in 113 (84%) of the patients in the leuprolide depot group and 74 (54%) of the patients in the danazol group ($p < 0.001$). Hot flushes appeared to be more severe in the leuprolide group, wherein 25 patients reported severe vasodilatation compared with nine patients in the danazol group ($p < 0.05$). The mean onset of vasodilatation symptoms averaged 29 days after the start of leuprolide depot administration and 35 days after the start of danazol administration; usually women who experienced hot flushes continued to experience them throughout the study. The clinical course of symptomatic vasodilatation follows the trial's observations of ovarian and menses suppression.[3]

Most patients reported side effects in addition to vasomotor symptoms: 122 (91%) of the patients who received leuprolide depot and 122 (90%) of the patients who received danazol reported additional adverse effects. Many side effects were similarly frequent between the two groups; particularly common were headaches, reported in 47 (35%) of the patients in the leuprolide depot group and 35 (26%) of the patients in the danazol group. Other common effects reported by the patients in the leuprolide depot group were vaginitis (29%), insomnia (17%), emotional lability (16%), nausea (13%), weight gain (13%), nervousness (13%), decreased libido (13%), acne (11%), depression (11%), and dizziness (10%). Patients in the danazol group reported acne (20%), vaginitis (19%), nervousness (16%), nausea (13%), depression (12%), emotional lability (11%), pain (10%), hypertonia (10%), seborrhea (6%), myalgia (5%), and visual disturbances (3%). The side effects in which prevalence differed significantly between the groups are presented in Table V.

Seven patients discontinued leuprolide because of adverse effects; five discontinued because of severe menopausal symptoms, especially nervousness and anxiety. One patient discontinued treatment because of eye pain, nausea and vomiting, hypertonia, and hot flushes; another discontinued because of clitoromegaly thought to be unrelated to the leuprolide.

Ten patients in the danazol group terminated participation in the study early because of adverse events; five discontinued because of skin rashes that occurred in the first month of treatment. It was not determined whether these rashes were acneiform or allergic in nature. For each of the following problems, there was one patient in the danazol group who terminated participation in the study: superficial thrombophlebitis, myalgia and arthralgia, severe depression, nervousness and emotional lability, and abdominal and leg pain.

Return of menses. In a follow-up of 101 of the patients in this study treated with leuprolide acetate depot, menstruation returned in all but two patients. One patient became pregnant shortly after completion of the treatment course, and the other was lost to follow-up before return of menses.

Comment

Danazol has been in common use for women with endometriosis since 1973, but its use is often associated with troublesome side effects and high rates of recur-

Table IV. Effects of leuprolide acetate depot versus danazol on serum chemistry values

Factor and normal range	*Drug*	*No.*	*No change from baseline*		*Returned to normal range*	*Increased beyond normal range*	*Decreased beyond normal range*
			No.	*%*			
Blood urea nitrogen (6-23 mg/dl)	Leuprolide acetate depot	117	109	93	7	1	0
	Danazol	108	101	94	3	0	4
Creatinine (0.6-1.7 mg/dl)	Leuprolide acetate depot	117	112	96	3	0	2
	Danazol	106	100	94	3	1	2
Serum glutamic-oxaloacetic transaminase (0-65 U/L)	Leuprolide acetate depot	117	111	95	1*	5*	0
	Danazol	106	89	84	3	14	0
Alkaline phosphatase (20-140 U/L)	Leuprolide acetate depot	116	110	95	2	4	0
	Danazol	106	99	93	0	1	6
Total bilirubin (0.2-1.4 mg/dl)	Leuprolide acetate depot	117	109	93	5	2	1
	Danazol	106	101	95	4	0	1
LDH (0-270 U/L)	Leuprolide acetate depot	114	102	89	5	7	0
	Danazol	104	85	82	10	8	1
Total protein (5.8-8.5 gm/dl)	Leuprolide acetate depot	116	104	90	4	5	3
	Danazol	106	99	93	4	3	0
Albumin (3.2-5.5 gm/dl)	Leuprolide acetate depot	116	109	94	3	4	0
	Danazol	107	99	93	2	3	3
Calcium (8.5-10.6 mg/dl)	Leuprolide acetate depot	117	111	95	4	2	0
	Danazol	107	102	95	1	3	1
Phosphate (2.1-4.5 mg/dl)	Leuprolide acetate depot	117	105	90	4	8	0
	Danazol	107	102	95	2	1	2
Urate (1.9-9.2 mg/dl)	Leuprolide acetate depot	114	104	91	6	1	3
	Danazol	107	97	91	5	1	4

*p = 0.028; all other between-drug comparisons not significant.

rent symptoms.[3] GnRH agonists were first used in clinical trials for endometriosis in 1981, and numerous clinical studies document consistent ovarian suppression with reduction of the severity and symptoms of endometriosis.[4, 5, 11-17]

Although the majority of patients taking either drug reported significant adverse effects, few women in either group withdrew from the study or otherwise manifested "severe" side effects. Similarly, no patient taking either drug was withdrawn because of a particularly unusual laboratory value. Leuprolide acetate depot was associated with more hypoestrogenic symptoms befitting its more complete ovarian suppression, whereas danazol is associated with more androgenic side effects.

The few changes in serum chemistry and hematologic parameters between the leuprolide and danazol groups were modest and probably of little clinical significance. The metabolic effects of these drugs on bone and lipid metabolism are of the greatest concern in terms of long-term toxicity.[17, 18]

Table V. Significant differences ($p < 0.05$) in adverse effects between leuprolide depot and danazol groups

Adverse effects	*Leuprolide depot group (n = 126)*		*Danazol group (n = 122)*	
	No.	*%*	*No.*	*%*
More frequent in leuprolide group				
Vasodilatation	113	84	74	54
Insomnia	23	17	8	6
Decreased libido	18	13	6	4
More frequent in danazol group				
Weight gain	17	13	36	27
Edema	7	5	24	18

Currently available methods of measuring bone density are imperfect because of inherent variations of ±2% to 5% for repeated measurements, with even greater variation likely between machines.[9, 19] Our study focused on "actual use" assessment of bone density by

each of the investigators with their standardized method of choice. In our study leuprolide acetate depot caused greater bone loss than did danazol. The degree of bone loss in our GnRH agonist group is similar to bone loss values reported by other investigators[17, 19-22] despite use of a variety of agonists and a variety of measurement techniques for measuring bone density. Although the bone loss associated with GnRH agonist use in endometriosis has been reported as being reversible,[4, 11] two strategies for minimizing loss may be shorter treatment (e.g., 3 months) or low-dose estrogen[18] or progestin[17] add-back during GnRH agonist treatment. There are few data yet regarding bone loss for shorter treatments, but experience with add-back strategies is expanding rapidly. Surrey and Judd,[17] for example, reported a significantly smaller decrease in bone density in women treated for 24 weeks with leuprolide acetate depot and an additional 5 to 10 mg daily of norethindrone ($-2.69\% \pm 0.94\%$) as opposed to women treated with leuprolide depot alone ($-5.57\% \pm 0.66\%$, $p < 0.05$). Further experience is necessary to determine which steroid might be preferable, as well as the appropriate dosage and length of time for its administration.

Lipid profiles changed according to the anticipated metabolic effects of each drug; changes in patients in the leuprolide group were associated with the symptoms of menopause, and changes in the patients in the danazol group were androgenic in nature. Other investigators[17] have shown that lipid values return to baseline within 60 days after cessation of therapy. The clinical significance of these apparently temporary changes in the lipid profile is unknown.

In summary, the methodological strengths of this randomized clinical trial allow several conclusions to be safely drawn. Leuprolide depot is as efficacious as danazol in the treatment of endometriosis, measured by change in the Revised American Fertility Society classification system and improvements in signs and symptoms.[6] Leuprolide depot induces more profound ovarian suppression than danazol does, which is demonstrated by the lower treatment levels of estradiol and the more rapid and complete cessation of menses.[5] Both drugs were frequently associated with a wide range of adverse effects, although few women discontinued their medication because of these effects. The greatest concern with GnRH agonist therapy is the documented decrease in bone density; although preliminary data suggest a return to baseline density over time, more longitudinal data on women treated with GnRH agonists are necessary before the possibility of long-term bone loss in some women can be excluded. Because of its high-density lipoprotein–lowering effect, danazol seems to be more of a concern than leuprolide acetate depot with respect to changes in the lipid profile. Again, more data are needed before a long-term health risk can be excluded. The risk of potential changes in bone or lipid metabolism will likely be reduced in the future by the addition of an estrogen or progestin "add-back."[17, 18]

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