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EFFECTS OF SUBCUTANEOUS ESTRADIOL IMPLANTS AFTER OOPHORECTOMY

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ABSTRACT

A prospective study was designed to determine the effectiveness of various doses of estradiol implants for estrogen replacement therapy after surgical castration. Seventy women were randomly assigned to one of the three treatment groups: 1) two 25 mg implants of estradiol, 2) one 25 mg implant of estradiol and one 25 mg implant of cholesterol (placebo) and 3) two 25 mg implants of cholesterol (placebo). Serum samples were obtained at monthly intervals for 6 months. Statistically significant differences between treatment groups were found with respect to menopausal symptoms, follicle stimulating hormone (FSH), estradiol (E2), and estrone (E1). However, for high and low density lipoproteins (HDL and LDL), cholesterol and antithrombin III, no statistically significant differences were found between groups. Although there was considerable variation between patients, the levels of FSH, estradiol and estrone were within the premenopausal physiologic range (follicular phase) in those patients receiving 25 or 50 mg estradiol implants. Vasomotor symptoms were noted in 88% of the group receiving placebo but were alleviated in 92% of the estradiol treated group.

INTRODUCTION

Implants of estradiol have been utilized since 1937 (Deansley/Parker, 1937), but it was not until Greenblatt/Surran's keystone publication in 1949 that they have been used on a large scale in menopausal patients. After being marketed for more than 20 years and bringing relief of vasomotor and other symptoms to thousands of climacteric women, they were not highly recommended in the early seventies for various reasons:

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a. The controversies surrounding the use of all types of estrogens because of their "potential carcinogenic side effects". These menacing rumors have cyclically invaded the medical literature.

b. The misuse of estrogens has caused breakthrough bleedings/endometrial hyperplasia in patients who were inadequately supplemented with oral progestogens.

c. The tightening of regulations and increased demands set forth by the FDA have made the release of any new drug on the market more difficult.

The main manufacturer (Schering Corporation) discontinued the production of all crystalline hormonal pellets and left the gigantic/intricate task of going through all the steps of licensure in the hands of smaller pharmaceutical companies. Having more than thirty combined years of therapeutic experience with the product and being convinced of its usefulness, we were contacted by Bartor Pharmacal in 1981 to design a study investigating the effectiveness/safety of estradiol implants. This study was performed on sixty patients undergoing surgical castration in 1982. The data was presented to the FDA in 1983 and has just been released by its sponsor (Bartor Pharmacal) for publication. Despite this unfortunate delay, the results are original and very much up to date.

The product has not yet been approved by the FDA for release in the market, despite the publication in the last decade of an exhaustive amount of research showing its usefulness, efficacy, safety and predictability (Brincat et al, 1988; Lobo et al, 1980; Notelovitz et al, 1987; Staland, 1978; Sturdee et al, 1978). The authors and other physicians experienced in using the estradiol implants have been impressed with the remarkable lack of side effects. Much of the research that has been done with estrogen implants comes from the United Kingdom where this mode of therapy was made popular by John Studd and co-workers from the King's College Hospital of London. Dr. Studd was recently quoted on why the use of pellets in the United States was "being incomprehensibly limited by the FDA" (Gambrell, 1987)!

MATERIALS / METHODS

Seventy women underwent hysterectomy and bilateral salpingo-oophorectomy for benign disease and were randomly assigned in double-blind

fashion into one of three treatment groups:

1. Estradiol 50 mg in the form of two Estrapel (Bartor) pellets (2E), 28 patients.
2. Estradiol 25 mg (one Estrapel pellet) and one placebo pellet (E+P), 25 patients.
3. Two placebo pellets (2P), 17 patients.

The placebo pellets each contained 25 mg of cholesterol. Each patient was evaluated prior to surgery, received her treatment and was further evaluated at monthly intervals for six months. All pellets were implanted subcutaneously one to ten days following surgery using aseptic technique and a Kearn's pellet injector. Patients could be released from the study if menopausal symptoms occurred. However, they were encouraged to remain in the study for a minimum of two months. The parameters of treatment efficacy recorded were:

a. serum concentrations of FSH, Estrone and Estradiol
b. number of patients requesting withdrawal from the study
c. number of months patients remained on the study
d. menopausal symptoms: at each visit, patients were asked whether they had any estrogen withdrawal symptoms such as hot flashes, sweating or irritability. Depending on their answer they were given a rating based on the following numerical values for symptoms:

none = 0, mild = 1 moderate = 2 severe = 3.

e. serum levels of cholesterol, high and low density lipoproteins, and antithrombin III were recorded for each visit. Before oophorectomy, the patients were indifferently pre- or postmenopausal. Follicle stimulating hormone (FSH), Estrone (E1) and Estradiol (E2) were measured in serum by radio-immunoassay. The laboratory reference ranges were as follows:

Hormone	Premenopausal	Postmenopausal
FSH	< 60 mIU/ml	>60 mIU/ml
E1	60-120 pg/ml	<60 pg/ml
E2	40-250 pg/ml	<30 pg/ml

Table 1. Demographic data quantitative variables

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Response	Statistic	2E	E+P	2P	p-value*
Age (years)	Mean	40.2	36.8	39.2	
	Std. Dev.	10.2	9.1	9.3	0.49
	n	28	25	17	
Height (inches)	Mean	64.0	64.5	63.5	
	Std. Dev.	2.7	1.8	1.9	0.38
Weight (pounds)	Mean	139.1	135.0	151.0	
	Std. Dev.	26.8	16.1	27.2	0.03

* Based on the analysis of variance

Table 2. Number of patients requesting withdrawal from the study

Treatment	
2E	1/28 (3.5%)
E+P	3/25 (12.0%)
2P	12/17 (70.0%)

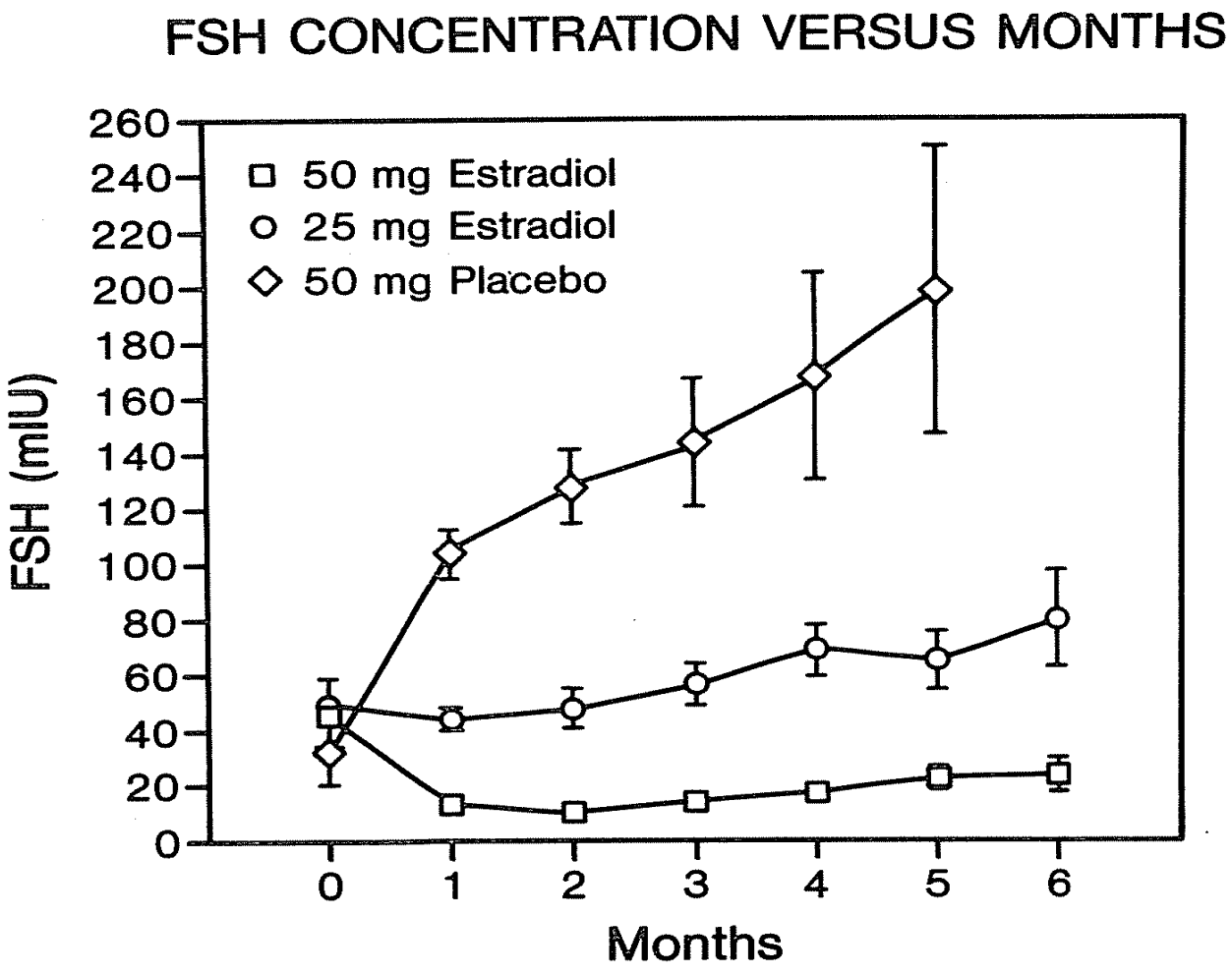

Figure 1. Variation in serum levels of FSH after oophorectomy and injection of 50 mg Estradiol, 25 mg Estradiol and placebo pellets. Values represent means (+/-S.E.) and are expressed in mIU/ml.

Cross-sectional comparisons between the treatment groups were made by analysis of variance using a two factor model (treatment and investigator). The frequency of patient withdrawal and number of patients with no symptoms was studied with a categorical linear model. Statistical significance was declared if the p-values were less than or equal to 0.05.

RESULTS

Table 1 summarizes the age, height and weight distribution for the patient population, broken down into treatment groups. No statistically significant differences were found with respect to age or height. The mean weight of the patients in the 2P group (151 lb) however, was higher than that of the patients in the 2E (139 lb) and E+P (135 lb) groups. Table 2 summarizes the number and percent of patients that requested withdrawal from the study. Among those in the placebo group, 70% of all patients requested to be withdrawn from the study. No patients in this group remained on the study the entire six month period. In comparison, only 3.5% withdrew from the 2E group and 12% from E+P group.

With respect to the number of months patients remained in the study, the average length of time was 3.2 months for the placebo group compared to 4.8 months for both the 2E and E+P groups. This difference was statistically significant. Those patients who did not ask to be released from the study were eventually given further treatment as the effect of their initial implant wore off. The length of time they stayed in the study; therefore, was directly proportional to the efficiency of the treatment.

Table 3 summarizes the number and percent of patients, for each month throughout the study, who experience no menopausal symptoms. Table 4 shows the menopausal symptom scores with a mean of 1.68 for the placebo group, compared to 0.86 for E+P group and 0.30 for the 2E group. There was a statistically significant decrease in the number of menopausal symptoms experienced in each of the treatment groups receiving estrogen replacement. The various hormone concentrations plotted against time are represented in Figures 1, 2 and 3. In the placebo group, the monthly FSH concentrations increased fairly regularly from the first month approaching approximately a six fold increase by the fifth month. Estrone and Estradiol levels declined precipitously during the six month period.

Table 3. Summary of menopausal symptoms. Number and percent of patients with no symptoms.

Month	2E	E+P	2P	p-value *
0	15/28 (54%)	11/25 (44%)	12/16 (75%)	0.18
1	24/28 (86%)	16/25 (64%)	4/16 (25%)	0.03
2	22/26 (85%)	15/23 (65%)	4/16 (25%)	0.03
3	19/23 (83%)	13/22 (59%)	3/7 (43%)	0.13
4	14/20 (70%)	8/20 (40%)	2/4 (50%)	0.11
5	8/16 (50%)	6/14 (43%)	2/3 (67%)	0.98
6	7/11 (64%)	1/8 (13%)	0/0	0.08

*Based on categorical linear model

Table 4. Summary of menopausal symptoms. Mean score per patient

Statistic	2E	E+P	2P	p-value*
Mean	0.30	0.86	1.68	
Std. Dev.	0.52	0.76	1.11	0.0001
n	28	25	16	

*Based on the analysis of variance

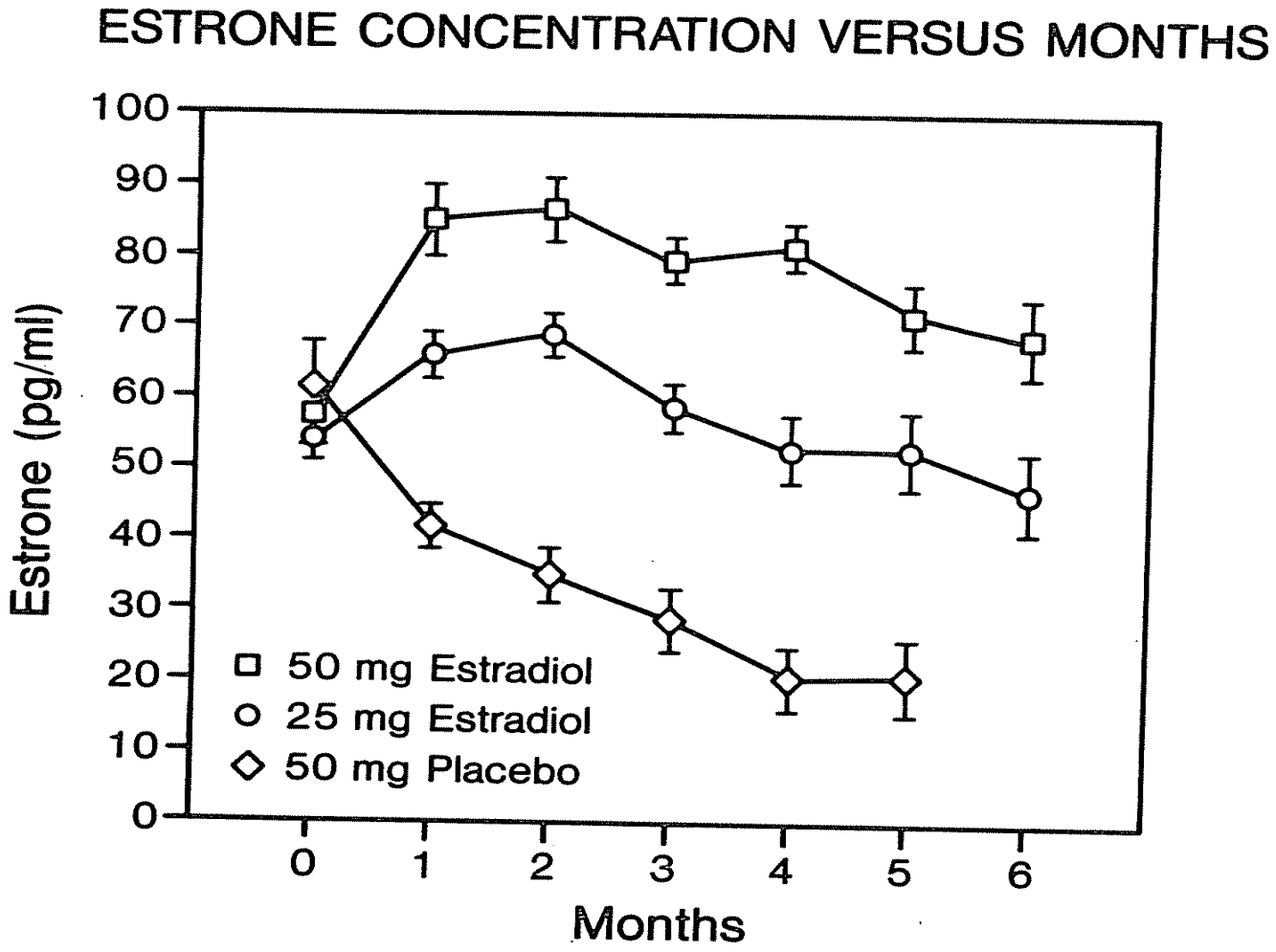

Figure 2. Variation in serum levels of Estrone after oophorectomy and injection of 50 mg Estradiol, 25 mg Estradiol and placebo pellets. Values represent means (+/-S.E.) and are expressed in pg/ml.

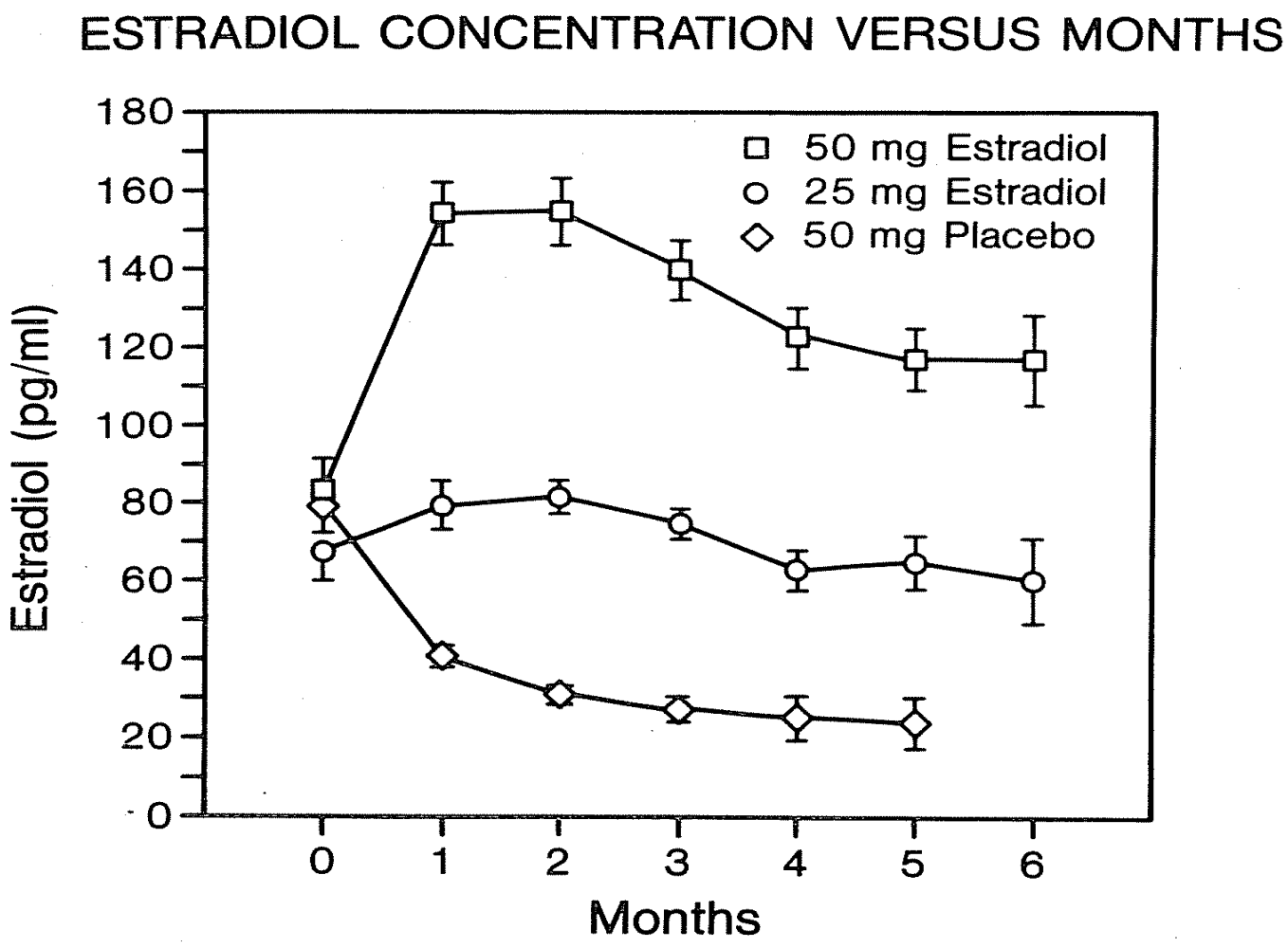

Figure 3. Variation in serum levels of Estraidol after oophorectomy and injection of 50 mg Estradiol, 25 mg Estradiol and placebo pellets. Values represent means (+/-S.E.) and are expressed in pg/ml.

In the estrogen replacement treatment groups, hormone levels showed more intersubject variability than in the placebo groups but the group means showed clear patterns of response. The FSH levels declined significantly in the 2E group and did not begin to rise until the fourth month. At the end of the six months, the levels were approximately one half their baseline values. Baseline values represent the pretreatment levels of the various analytes. Since both pre- and postmenopausal patients were included, these levels represent a wide range of physiological states. Baseline levels here are used as a somewhat artificial median level against which the effect of the treatment can be compared. The E+P group showed little change in FSH levels for the first two months but thereafter gradually increased to about one and a half time the baseline value by six months. In the 2E group, Estrone and Estradiol levels increased rapidly during the first month, began to decline in the third month but were still at least 20% above baseline values after six months.

In the E+P group, Estradiol levels showed an irregular increase from baseline resulting in a final concentration at 6 months approximately 20% higher than baseline. Estrone increased during the first two months and then declined irregularly and were below baseline by the six month of treatment.

Concentration of cholesterol, high and low density lipoproteins and antithrombin III are graphically displayed in Figures 4 to 7. The slight changes in high and low density lipoproteins as well as in antithrombin III levels were not significant. The slight rise in serum cholesterol level that was seen in the placebo group is not unusual following oophorectomy. However, in the estrogen replacement treatment groups similar increases were not seen. The cholesterol concentrations in these groups remained very constant throughout the study. The wide range in standard errors in the placebo group regarding lipids and antithrombin III is explained by the decreasing number of patients. Ten out of 17 had asked to withdraw from the study before 3 months and only 3 patients remained in the study until the fifth month.

This study did not demonstrate any adverse effects as a result of this treatment. Only one patient in the 2E group complained of breast tenderness.

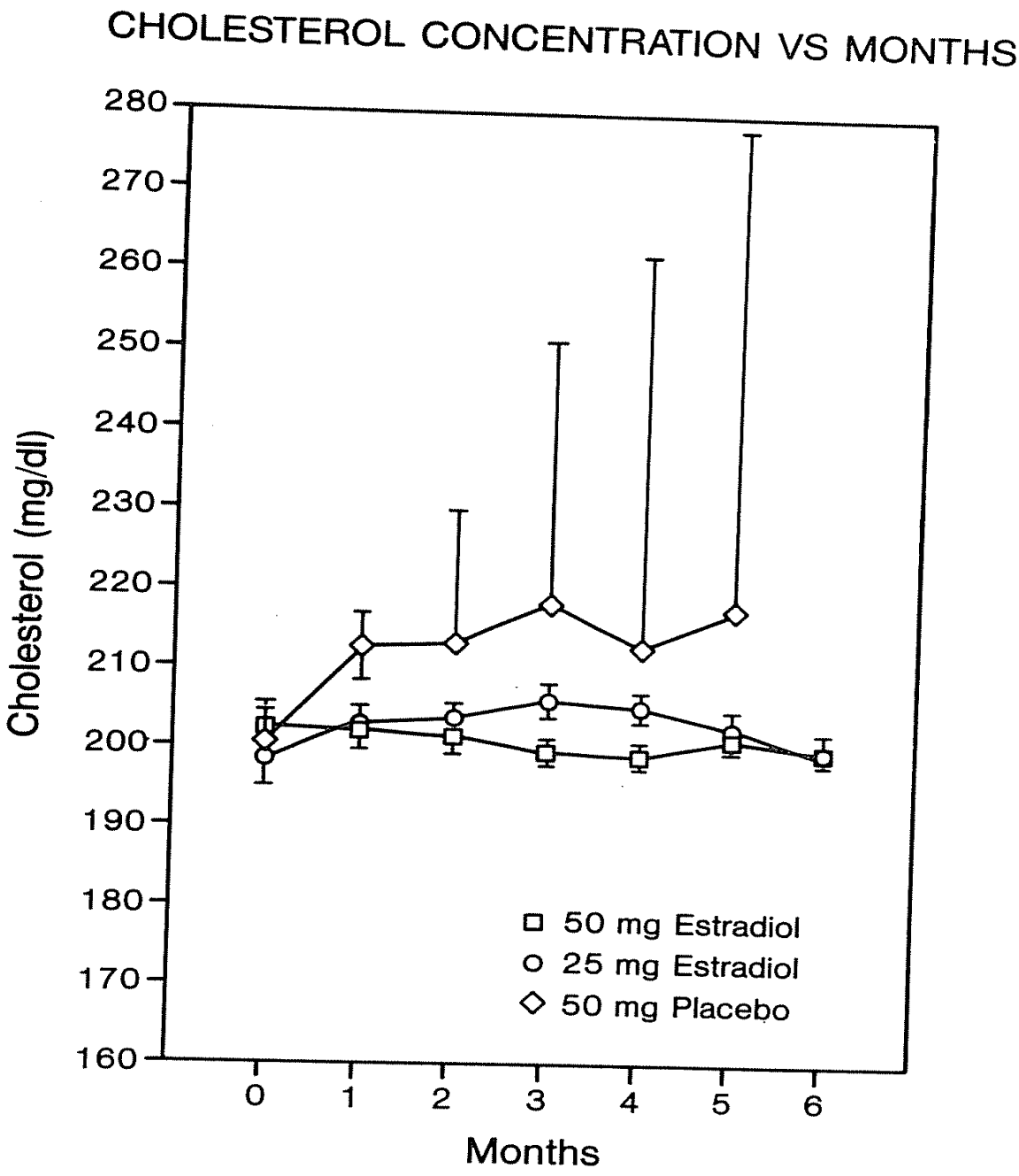

Figure 4. Variation in serum levels of Cholesterol after oophorectomy and injection of 50 mg Estradiol, 25 mg Estradiol and placebo pellets. Values represent means (+/-S.E.) and are expressed in mg/dl.

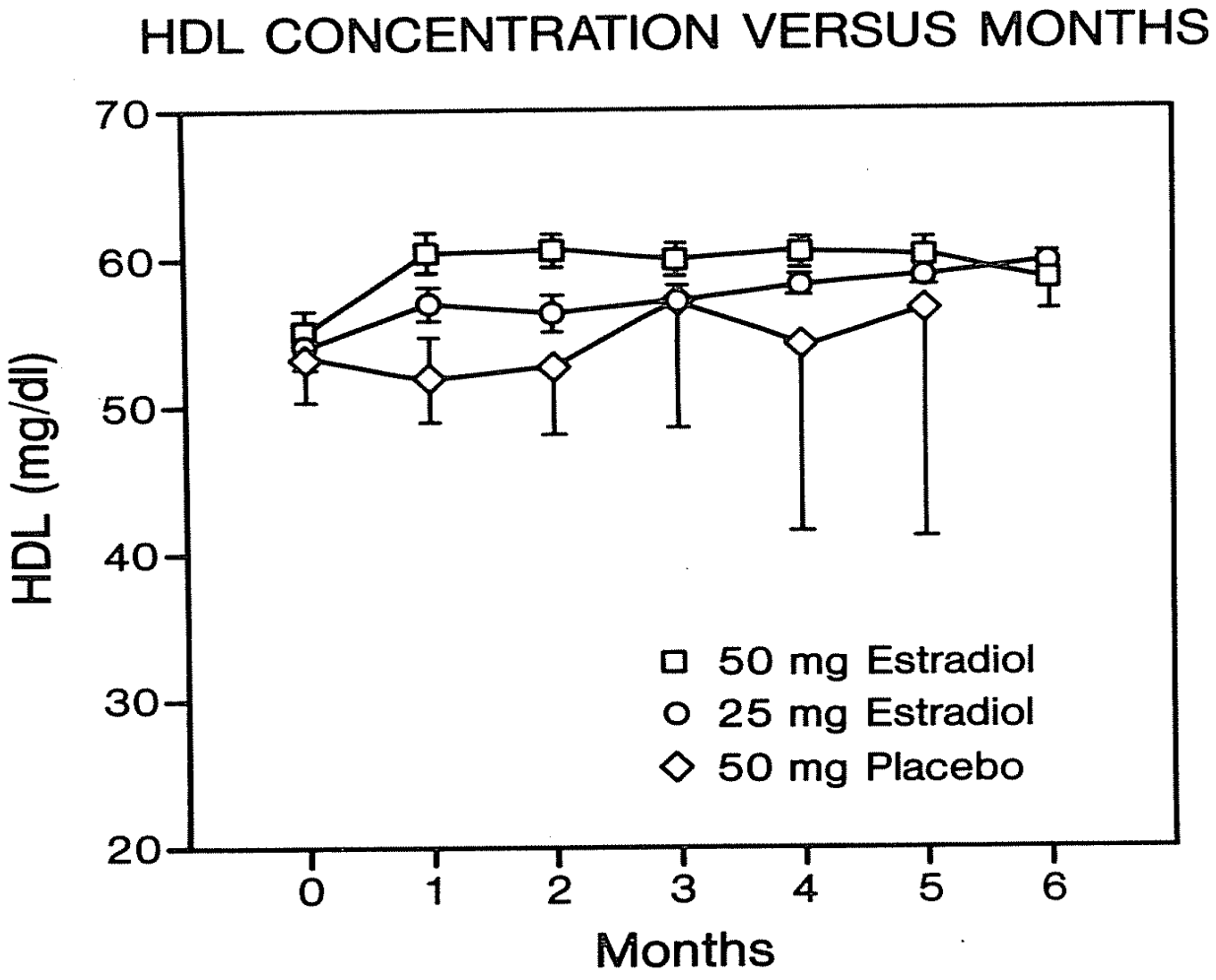

Figure 5. Variation in serum levels of HDL after oophorectomy and injection of 50 mg Estradiol, 25 mg Estradiol and placebo pellets. Values represent means (+/-S.E.) and are expressed in mg/dl.

DISCUSSION

Subcutaneous crystalline implants of 17 beta-estradiol are biodegradable and provide a very effective method of estrogen replacement therapy. Acceptance by the patients has been excellent, which has not always been the case with other parenteral methods of pure estradiol administration (percutaneous patches, gel and vaginal cream). Only one (3.5%) woman asked not to continue therapy when receiving 50 mg of estradiol and 3 (12%) when taking 25 mg. Twelve out of 17 patients receiving placebo asked to withdraw from the study and were administered other medication to treat their hot flashes.

Parenteral estradiol has several metabolic advantages over oral equivalents:

1) Portal circulation and "first pass" effect on liver metabolism is avoided. Oral estrogens are largely metabolized and inactivated before reaching the systemic circulation (Elkik et al, 1982)

2) The gastrointestinal tract, where the major conversion of estradiol to estrone takes place, is by-passed (Ryan/Engal, 1953; Cedars/Judd, 1987)

3) Estradiol is biologically much more active than estrone, the main constituent of conjugated estrogens.

4) A large bolus of steroids entering the portal circulation caused by rapid intestinal absorption is avoided (Lyrenas et al, 1981)

5) Ease of the treatment: Many patients would rather receive an implant on a semiannual basis at the time of their medical check-up than be submitted to a burdensome daily oral regimen.

The serum levels of estradiol/estrone were within the range expected for premenopausal women whether they were receiving 25 or 50 mg of estradiol. Such predictability has been confirmed (Lobo et al, 1980; Notelovitz et al, 1987; Staland, 1978; Magos et al, 1987). Other authors have warned that obesity could cause lower estradiol in fat and/or the greater and altered peripheral conversion in obese women (Fishman et al, 1975). We were not able to make such an observation but there may not have been enough weight variation between treatment groups to obtain significant difference. If anything, our placebo group was heavier than the other two treatment groups, and it did not seem to have interfered with the expected decline from baseline in estradiol levels.

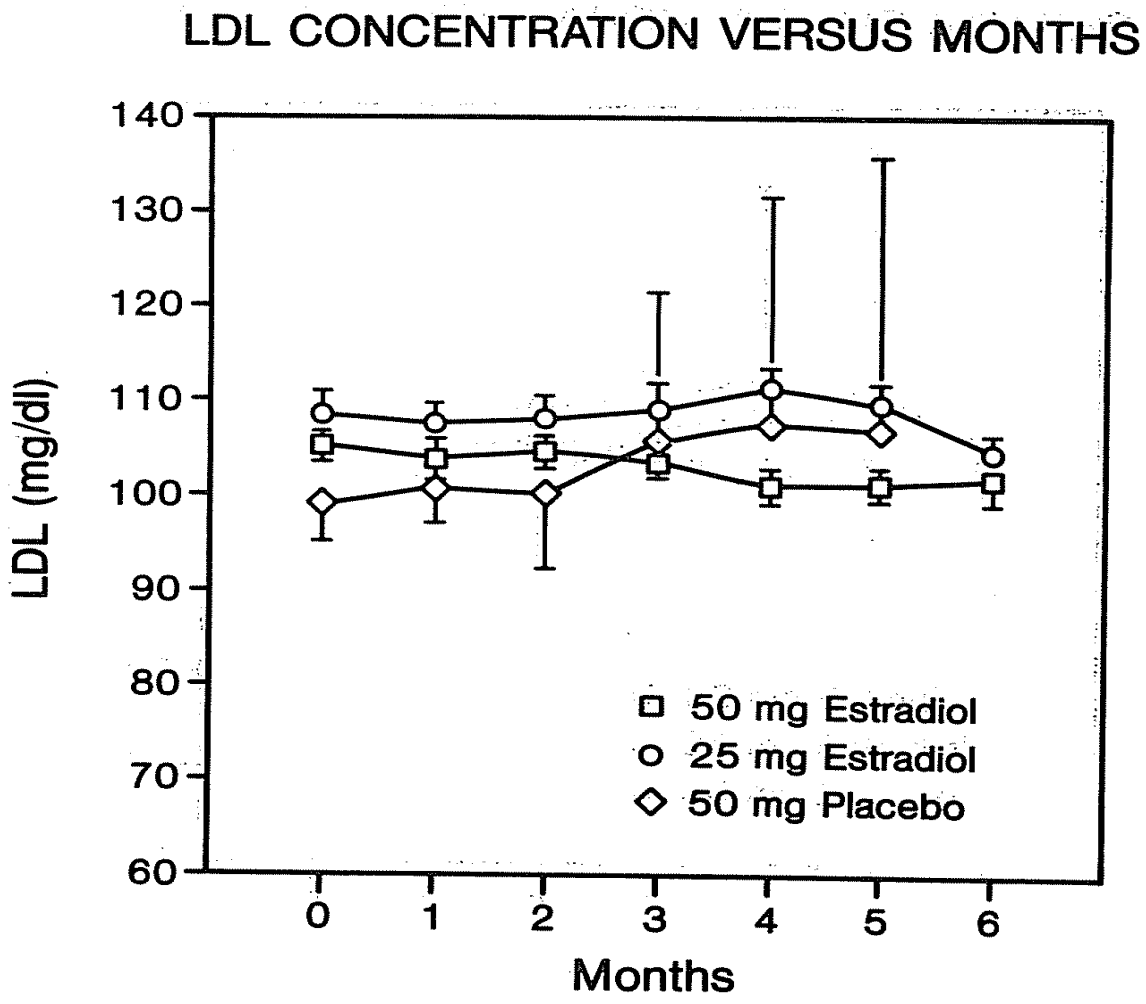

Figure 6. Variation in serum levels of LDL after oophorectomy and injection of 50 mg Estradiol, 25 mg Estradiol and placebo pellets. Values represent means (+/-S.E.) and are expressed in mg/dl.

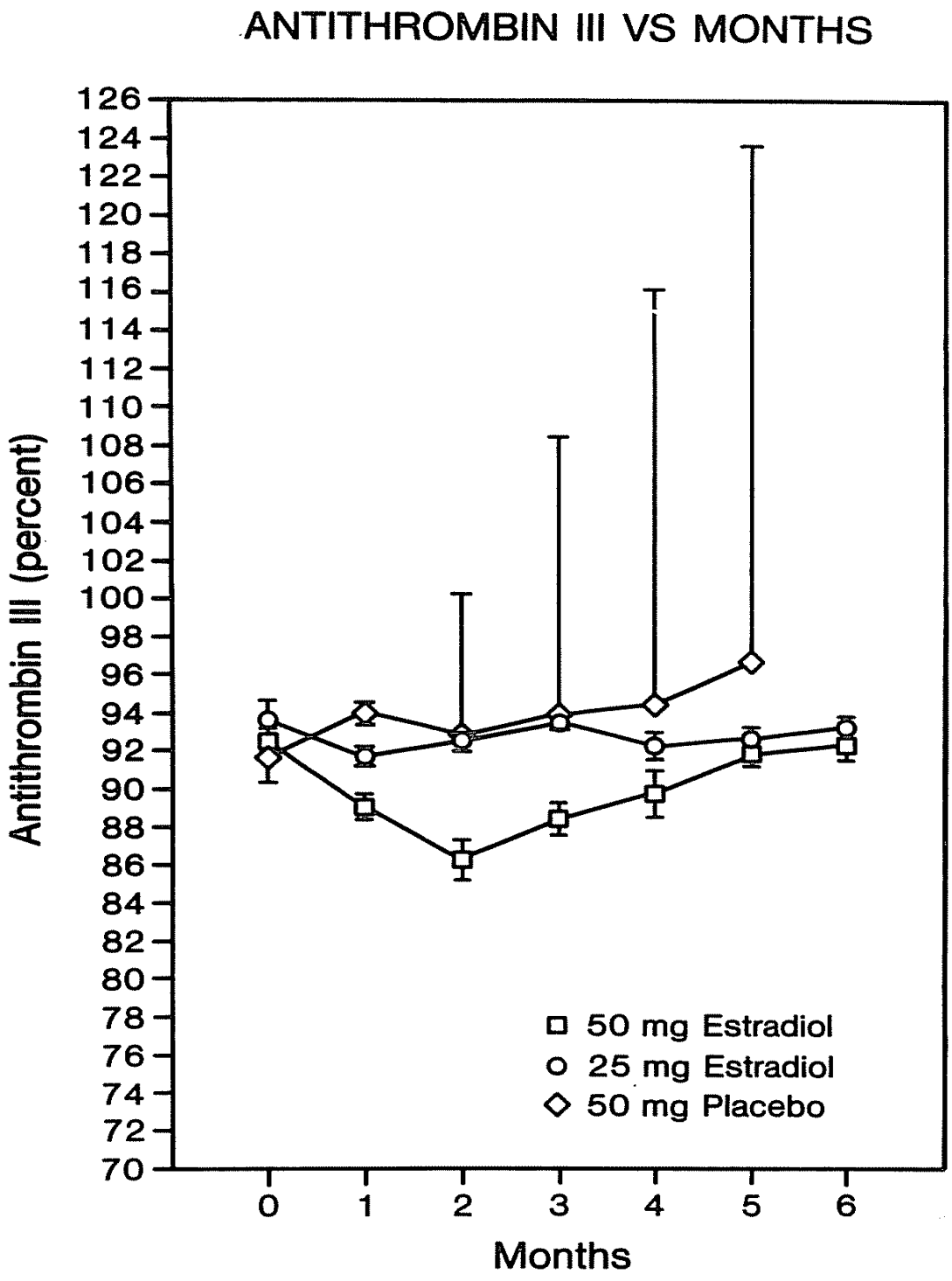

Figure 7. Variation in antithrombin III after oophorectomy and injection of 50 mg Estradiol, 25 mg Estradiol and placebo pellets. Values represent means (+/-S.E.) and are expressed in percentages.

Although patients generally complain 5 to 6 months after implantation of a slow but steady return of their original menopausal symptoms, our study shows a persistent release of estradiol even six months after treatment. Other studies have shown that the effects of estradiol pellets could be still detected 12 months to 2 years later especially if larger doses (above 50 mg) were administered (Studd et al, 1987). If the treatments are repeated every six months, an accumulative effect may take place with a progressive rise of estrone and estradiol concentrations (Cardozo et al, 1984). In order to avoid such a potential build up, it is our recommendation to recheck the estrogen levels before each, and every subsequent treatment so that the amount of estradiol implanted may be adjusted accordingly. One solution to the potential drawback of build up or adverse reactions would be the removal of the pellet. Despite efforts made by various researchers, no one has yet discovered a way to trace the pellet within the subcutaneous tissue. Any attempt to retrieve them would probably be fruitless and should be strongly discouraged.

This study was designed, following FDA guidelines, in such a way that any risks of stimulating the endometrium would be avoided. However, despite the link between unopposed estrogen therapy and endometrial carcinoma, treatment with all types of parenteral estradiol has proven safe in pre- and post menopausal women provided it is used in conjunction with cyclic oral progestogen (Sturdee et al, 1978; Studd et al, 1987). It would appear that the endometrial protection afforded by progestogens is duration (ten or more days each month) rather than dose dependent (Sturdee et al, 1978). The other main target organ is the breast, which also seems safe according to a recent compilation of the literature on this subject by Gambrell who concluded:

> "There is no evidence that estrogens increase the risk of breast cancer while the addition of progestogen seems to reduce the incidence" (Gambrell, 1987).

Elevated serum cholesterol, especially its LDL fraction, has been linked to a greater risk for ischemic heart disease. The most recent consensus is that parenteral, and more so, oral estrogen compounds produce favorable changes in lipid metabolism, protective against cardiovascular disease (Notelovitz et al, 1987; Fahreus et al, 1982; Farrish et al, 1984). In our study, serial measurements of cholesterol, high and low density lipoproteins have failed to

demonstrate any conclusive treatment effect of the estradiol pellets on any of these variables.

Estrogen, particularly the synthetic kind such as ethinyl estradiol, has been blamed for inducing adverse changes in the clotting and fibrinolytic systems. Macromolecules such as renin substrate and antithrombin III which depend on hepatic metabolism have been implicated in the development of hypertension and venous thrombosis with oral therapy (Elkik et al, 1982). Parenteral administration of estradiol, which has a minimal effect on hepatic protein synthesis, would therefore appear to be beneficial. In this study, although no statistically significant differences were found, there appears to be a slight decrease in antithrombin III during the first 4 months following pellet insertion, when the full dose of estradiol (50 mg) is given. This trend was not confirmed in the treatment group receiving only the half dose (25 mg) of estradiol.

Effects of estrogen on hepatic protein can also be evaluated/determined by measurement of sex binding globulin (TEBG). We have observed, as it has been reported by others that synthetic and conjugated oral estrogens increase the levels of TEBG and the estradiol pellets do not (Lobo et al, 1980).

Although it was not the objective of our study, other beneficial effects of the estradiol pellets deserve to be noted:

1. In the treatment of psychological disorders in the climacteric (anxiety, distress, depression) (Montgomery et al, 1987).
2. In the prevention of postmenopausal osteoporosis (Lobo et al, 1980) with also a greater skin collagen content and thickness by comparison with untreated women (Brincat et al, 1988). Other types of parenteral/oral estrogens are also efficient in the prevention of osteoporosis and psychological disorders which would have a detrimental and crippling effect in this large segment of our female population. It is remarkable, as formerly observed by Staland (1978), that such small amounts of estrogen (as with estradiol pellets) are required to keep the patients free of symptoms. With an effective duration of 6 months, the daily dose of estradiol can be calculated at approximately 0.1 mg compared with about 0.3 mg for injections of long acting estradiol esters and 0.5 and 2 mg with oral administration. The relatively low but constant estrogen levels may attribute to the good tolerance of the treatment and well-being generally acknowledged by the patients.

In conclusion the use of estradiol pellets is a very effective, safe and predictable method of estrogen replacement therapy. Its benefits and conveniences far outweigh any potential drawbacks. It is better accepted by the patients than other parenteral methods of estradiol administration. Its bypass of liver function/gastrointestinal tract provide undeniable and important advantages over all oral estrogens.

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