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Subdermal estradiol pellets following hysterectomy and oophorectomy

Effect upon serum estrone, estradiol, luteinizing hormone, follicle-stimulating hormone, corticosteroid binding globulin–binding capacity, testosterone-estradiol binding globulin–binding capacity, lipids, and hot flushes

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Subdermal estradiol (E_2) pellets (25 mg) were inserted immediately after hysterectomy and oophorectomy in 22 menstruating women, ages 29 to 50 years. Serum samples were obtained daily for 7 days, weekly for 4 weeks, and at monthly intervals for 6 months. Although there was significant variation between patients, E_2 levels remained within the follicular phase range, averaging 50 to 70 pg/ml for 3 months, and then slowly declining to a mean of 37 pg/ml at 6 months, when new pellets were inserted. Over the entire study period, the E_2:estrone (E_1) ratio was greater than unity. Subdermal E_2 pellets limited the rise in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) after gonadectomy and the levels of LH and FSH 6 months after the insertion of E_2 pellets were significantly lower ($p < 0.01$) than in 20 postmenopausal women who had undergone oophorectomy and whose serum E_2 levels were less than 20 pg/ml. Serum corticosteroid binding globulin–binding capacity (CBG-BC) and serum testosterone–estradiol binding globulin–binding capacity (TeBG-BC) remained unchanged with E_2 pellets. Although high-density lipoprotein–cholesterol increased significantly ($p < 0.05$), low-density lipoprotein–cholesterol, total cholesterol, and triglycerides were unaffected, except for a rise in triglycerides in three older women with diabetes mellitus and hypertension. There were no complaints of severe hot flushes. Women who had vasomotor symptoms had mild or moderate flushes that occurred at 5 or 6 months after replacement of the pellets. Thus, E_2 pellets are an effective form of parenteral estrogen replacement therapy and offer both practical and theoretical advantages over other forms of estrogen replacement. (AM. J. OBSTET. GYNECOL. 138:714, 1980.)

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NUMEROUS estrogen preparations and modes of administration have been developed in an effort to find which will relieve climacteric symptoms and prevent osteoporosis. Among the forms of therapy, subdermal implants of crystalline estradiol (E_2) have been used since 1938.[1-6] Both relief of vasomotor symptoms and the patient's preference over oral or parenteral estrogen therapy have been reported.[7] However, there is a paucity of data in regard to the levels of estrogen and gonadotropins after implantation of E_2 pellets. Hunter and associates[8] studied 23 patients for 15 months after

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the administration of one E_2 pellet containing 100 mg. Because the serum levels of E_2 exceeded those attained during the midfollicular phase of the cycle, it was apparent that only a lower dose could provide physiologic levels of E_2. The purpose of this study was to investigate the effects of the subcutaneous placement of one 25 mg E_2 pellet at the time of gonadectomy upon serum levels of estrogens, gonadotropins. lipids, and binding proteins and upon hot flushes, for a 6-month period.

Material and methods

The study group consisted of 22 women, ages 29 to 50 years, who underwent a hysterectomy and bilateral salpingo-oophorectomy because of severe salpingitis, leiomyomata uteri, or persistent menorrhagia or menometrorrhagia. Prior to operation, 15 women had ovulatory menstrual cycles and seven were anovulatory, but all had serum levels of follicle-stimulating hormone (FSH) or luteinizing hormone (LH) which were within the normal follicular phase range. All the patients elected to use E_2 pellets for replacement therapy. One 25 mg crystalline E_2-17β pellet (Progynon) was inserted subdermally with a trocar through a separate skin incision adjacent to the laparotomy incision after closure of the laparotomy incision.

Blood samples were obtained 1 day prior to operation and at 6 and 12 hours after insertion of the pellet and then daily at 9:00 A.M. for 7 days, weekly for the first month, and then monthly for 6 months. The serum samples obtained before and at 1, 2, 3, and 4 weeks and at 2, 3, 4, 5, and 6 months after implantation of the pellet were analyzed in all women. In addition, the blood drawn during the first week after insertion of th pellet was analyzed for E_2 in 10 women randomly selected from among the 22 patients. Serum lipids were analyzed in only 12 patients. LH and FSH were assayed in only 15 patients.

The results obtained from analyses of the sera of these women were compared to those obtained from a control group of 20 postmenopausal women, ages 50 to 60 years, who had undergone hysterectomy and bilateral salpingo-oophorectomy at least 2 years earlier. Although the ages of these women differed from those of our study patients, their weights were similar. Despite the fact that none of these control women was followed immediately after operation, there is ample evidence in the literature that hormonal levels are in the postmenopausal range 2 weeks after oophorectomy.[9] The samples of blood from these postmenopausal women were obtained after an overnight fast. None had taken any estrogen-containing compounds for at least 3 months. In addition, three of these 20 postmenopausal

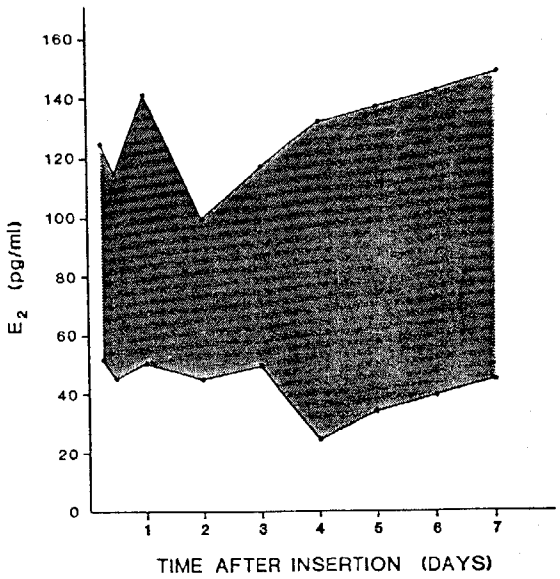

Fig. 1. The range of serum estradiol (E_2) concentrations during the initial 7 days after the insertion of one 25 mg E_2 pellet in 10 premenopausal women who underwent hysterectomy and oophorectomy.

women volunteered to ingest 10 μg of ethinyl estradiol (EE_2, Estinyl) for 2 weeks. Twenty-microgram capsules of Estinyl were carefully divided in half and weighed on a microbalance to assure equal weights of each half. Venous blood for analysis was drawn prior to and at the end of the intake of EE_2. Blood was also obtained from another three of the 20 women before and after they had ingested conjugated estrogens (Premarin), 0.625 mg daily for 2 weeks.

In every instance, the blood was allowed to clot and the serum was separated and stored at −20° C for no longer than 3 months. Assays were carried out on these samples by means of procedures previously described for E_2 and E_1[10] and LH and FSH.[11] Determination of corticosteroid binding globulin–binding capacity (CBG-BC)[12] and testosterone-estradiol binding globulin–binding capacity (TeBG-BC) was carried out in our laboratory[13] with a modification of the method of Rosner[14] based on the binding of TeBG in plasma to tritiated dihydrotestosterone. Total cholesterol and total triglycerides were determined enzymatically with the use of a system Gilford 3500 computer-directed analyzer (Gilford Instruments, Oberland, Ohio). High-density lipoprotein(HDL)–cholesterol was measured enzymatically after precipitation with sodium phosphotungstate and magnesium chloride.[15] Low-density lipoprotein(LDL)–cholesterol was calculated.[16] All assays from each individual patient were performed at the

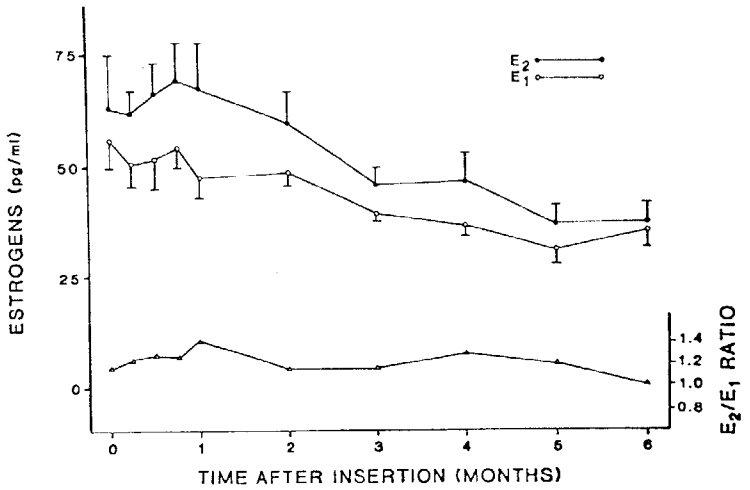

Fig. 2. Mean (±SE) serum estradiol (E_2) and estrone (E_1) levels and E_2/E_1 ratios in 22 women after oophorectomy and insertion of one 25 mg E_2 pellet.

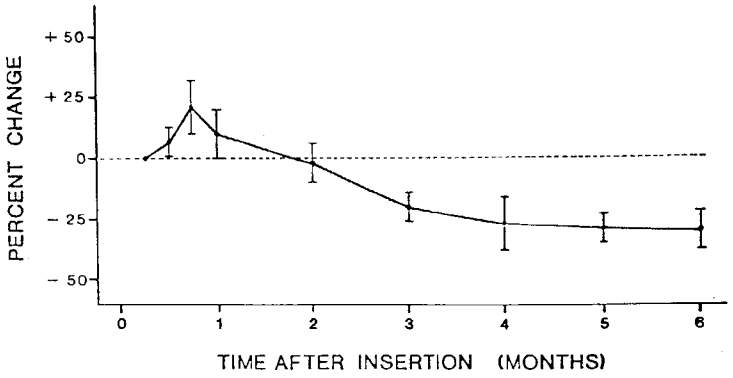

Fig. 3. Variation in serum levels of estradiol (E_2) after oophorectomy and insertion of a 25 mg E_2 pellet in 22 women. Values represent means (±SE) of each women's E_2 level expressed as percent of her serum E_2 level 7 days after insertion of the pellet. Values are expressed as percent change.

same time in order to decrease interassay variability.

No women received any medications chronically. Ten women received short-term, broad-spectrum antibiotic therapy in the first 7 to 10 days postoperatively. In this study, measurements on blood were carried out mainly after this first week. One woman took an oral hypoglycemic agent (tolbutamide) sporadically.

Information about the frequency and severity of hot flushes was obtained by oral questions at the time of each patient's visit and was characterized as mild, moderate, or severe. Occasional flushes which did not affect the patient's daily routine were defined as being mild. Moderate flushes were defined as those which occurred more often than twice per day and were troublesome but did not affect the patient's routine. Severe flushes were characterized as being frequent and affecting daily routines, so that the patient was led to seek medical assistance. Paired t tests were used to judge statistical significance.

Results

The range of E_2 levels during the first 7 days after insertion of the pellet in 10 women is indicated in Fig. 1. After oophorectomy and subdermal placement, the pellet released E_2 slowly. There was no initial "burst" effect, and serum E_2 levels remained below 150 pg/ml in the first 7 days after implantation.

It was found that the mean level of E_2 rose gradually and was highest 3 weeks after insertion of the pellet and then declined slowly thereafter (Fig. 2). Mean E_1 levels were relatively stable for 2 months and then declined gradually. Therefore, the ratio of E_2 to E_1 re-

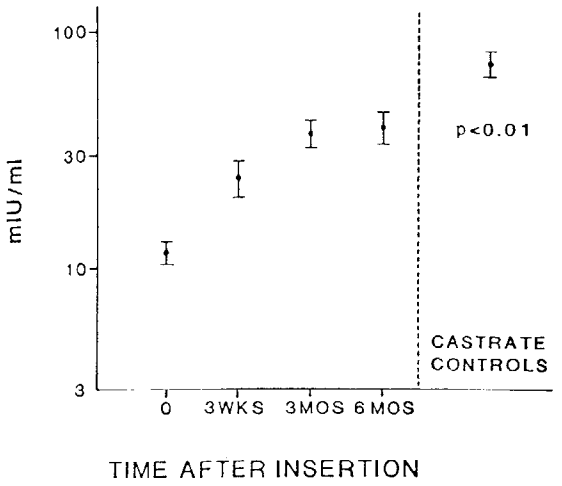

Fig. 4. Mean (±SE) serum LH levels (in mIU/ml) prior to and after oophorectomy and insertion of a 25 mg estradiol pellet in 15 premenopausal patients. The panel on the right depicts serum LH levels in 20 postmenopausal oophorectomized women not receiving estrogens.

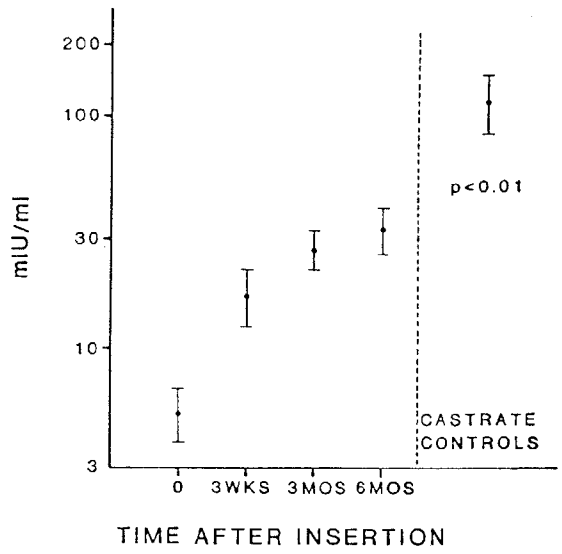

Fig. 5. Mean (±SE) serum FSH levels (in mIU/ml) prior to and after oophorectomy and the insertion of a 25 mg estradiol pellet in 15 postmenopausal women. The panel on the right depicts serum levels of FSH in 20 postmenopausal women not receiving estrogens.

mained greater than one throughout the study period. Estradiol levels in the postmenopausal control group were less than 20 pg/ml.

Estradiol levels varied widely among patients. Three weeks after implantation of the pellet, E_2 levels ranged from 30 to 122 pg/ml. Nevertheless, there was little variation in E_2 levels (expressed as percent change) within each patient during the 6 months (Fig. 3). When the individual values during 6 months were compared to the level attained 1 week after insertion of the pellet, the mean variation was found to be less than 30%. LH and FSH levels (in mIU/ml expressed as mean ± SEM) remained within the normal range for the first 3 weeks after implantation of the pellet and then rose progressively (Figs. 4 and 5). However, even 6 months after insertion of the pellet, LH and FSH levels were significantly lower than those of postmenopausal controls ($p < 0.01$). There was no significant change in the mean ± SEM CBG-BC in the patients with a pellet (Fig. 6). Two weeks of treatment with 0.625 mg of conjugated estrogens daily did not increase CBG-BC; however, 10 μg of ethinyl estradiol per day did cause a significant increase in CBG-BC ($p < 0.05$).

The mean ± SEM TeBG-BC also remained normal in the women who had a pellet, but both conjugated estrogens and ethinyl estradiol induced a significant elevation of TeBG-BC ($p < 0.05$) (Fig. 7).

HDL-cholesterol levels increased significantly ($p < 0.05$), whereas LDL-cholesterol and total cholesterol were not significantly altered (Fig. 8). For the patients as a group, total triglycerides were significantly in-

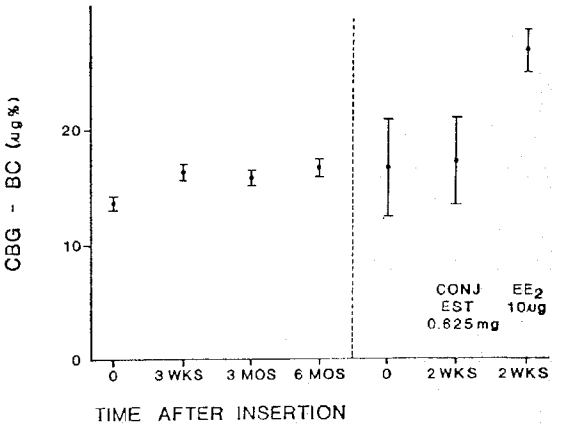

Fig. 6. Mean (±SE) CBG-BC, in μg%, prior to and after oophorectomy and the insertion of a 25 mg estradiol pellet in 22 women. The panel on the right shows the effect of 0.625 mg of Premarin and 10 μg of Estinyl (EE_2) on CBG-BC in six postmenopausal women.

creased ($p < 0.05$). However, this increase was due to a marked elevation (percent increase of 585, 414, 394) which occurred in three women who had both hypertension and diabetes mellitus. None of the subjects had severe hot flushes during the 6 months of treatment with the pellets (Table I). Five women never had a hot flush, whereas eight had mild hot flushes and nine had moderate flushes, primarily in the fifth and sixth months after insertion of the pellet.

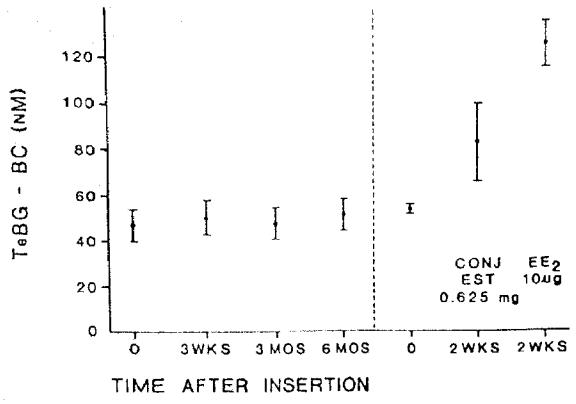

Fig. 7. Mean (±SE) TeBG-BC, in nM, prior to and after oophorectomy and insertion of a 25 mg estradiol pellet in 22 women. The panel on the right shows the effect of 0.625 mg of Premarin and 10 μg of Estinyl (EE_2) on TeBG-BC in six additional postmenopausal women.

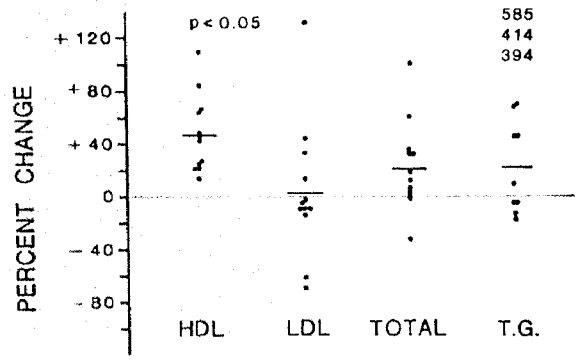

Fig. 8. Precent changes in serum lipids at 3 months compared to preoperative levels in 12 women undergoing oophorectomy and the insertion of a 25 mg estradiol pellet. Three women with diabetes mellitus and hypertension had markedly elevated serum triglycerides (394% to 585% change) and are depicted separately. *HDL*, high-density lipoprotein-cholesterol; *LDL*, low-density lipoprotein-cholesterol; *Total*, total cholesterol; *T.G.*, total triglycerides.

Comment

This study describes the effect of continuous estrogen replacement therapy by means of a subdermal pellet containing 25 mg of crystalline E_2. This mode of therapy offers several advantages. Release of E_2 from crystalline pellets is rapid and fairly constant during the life span of the pellet. In contrast, oral administration of estrogen causes markedly elevated serum estrogen levels which are observed immediately and which are then followed by low levels. When E_2 is administered parenterally, it reaches all tissues without prior passage through the liver, so that the effective hepatic conversion of E_2 to E_1 is less than that which occurs after oral therapy. Thus, the E_2 to E_1 ratio remains greater than one as it occurs during normal ovarian function. Serum E_2 and E_1 levels remain within normal early and midfollicular phase ranges for at least 6 months.

Table I. Complaint of hot flushes after oophorectomy and the insertion of a 25 mg estradiol pellet in 22 women

	Months					
Hot flushes	*1*	*2*	*3*	*4*	*5*	*6*
None	20	22	21	20	5	5
Mild	2	0	0	1	10	8
Moderate	0	0	1	1	7	9
Severe	0	0	0	0	0	0

Acceptance by the patient of this method was excellent. At the end of 6 months, only two women preferred not to continue therapy with the E_2 pellet, for personal reasons. Hot flushes were never severe and initially occurred 4 or more months after implantation of the pellet.

Only one 25-mg E_2 pellet was used in this study. Various authors have used two or more pellets at a time[8, 17]; however, in an earlier study, we found that one 25 mg pellet was sufficient to achieve adequate serum E_2 concentrations.[8]

Although E_2 levels after insertion of the pellet remained fairly constant within each patient, they varied widely among different subjects. This is at least partly related to the distribution of body fat. In this study, the more obese the woman, the lower were the total serum E_2 levels ($p < 0.05$). This effect may have been related, in part, to the sequestration of E_2 in fat and, in part, to the greater and altered peripheral conversion in obese women.[19]

Treatment with subdermal E_2 pellets results in a more protracted rise in serum LH and FSH after oophorectomy. Serum levels of LH and FSH remained within the normal premenopausal range for 3 weeks and then became elevated. However occasional individual values were still in the normal premenopausal range at 6 months. No correlation was found between individual levels of E_2 and gonadotropins in any one patient.

CBG is a hepatic protein whose binding capacity is known to correlate with increasing levels of estrogen.[20] In this study, E_2 pellets did not affect the levels of CBG-BC, in contrast to the significant increase produced by the ingestion of a small amount of ethinyl estradiol.

Serum TeBG-BC is a more sensitive indicator of the

effects of estrogen upon hepatic proteins.[21] Although both the conjugated and synthetic oral estrogens increased the levels of TeBG-BC, the E_2 pellets did not alter the levels from baseline.

With regard to serum lipids, LDL-cholesterol and total cholesterol remained essentially unchanged. Total triglycerides increased in the patients as a group, but this was secondary to an effect upon three women. These greatly increased levels of triglycerides occurred in older women, ages 47, 48, and 50. All three had hypertension and either overt diabetes (one) or chemical diabetes mellitus (two). One of these women was receiving an oral hypoglycemic agent. In these three women, HDL, LDL, and total cholesterol were in the normal ranges, and triglyceride levels were only elevated at 3 months. The values at 3 months ranged from 347 to 677 mg/dl. Careful monitoring of such patients is needed if estrogen therapy is to be used.

In conclusion, the use of E_2 pellets is an effective, well-tolerated, and safe parenteral form of estrogen replacement therapy. It offers many practical and theoretical advantages over other forms of replacement therapy.

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