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## A randomized comparison of nonoral estradiol delivery in postmenopausal women

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We compared the transdermal and subdermal routes of estrogen administration with respect to the constancy of estrogen delivery and metabolic effects. Twenty postmenopausal women were randomized to receive either two 25 mg estradiol pellets subdermally ( $n = 10$ ) or a 0.1 mg estradiol transdermal patch twice weekly ( $n = 10$ ). Blood was sampled at 0, 2, 4, 6, 8, 12, 24, and 72 hours and 1, 2, 4, 8, 12, 16, 20, and 24 weeks (fasting samples at 0, 12, and 24 weeks), and a fasting urine was obtained after diuresis at 0, 12, and 24 weeks. In a 72-hour profile, serum estradiol levels (mean  $\pm$  SE) were highest at 24 hours ( $179 \pm 20$  pg/ml) and fell to  $139 \pm 16$  pg/ml at 72 hours in the pellet group. In the patch group, estradiol levels rose rapidly to  $152 \pm 33$  pg/ml at 4 hours, remained relatively constant over 8 hours, and fell to  $46 \pm 10$  pg/ml at 72 hours. At 1 week, estradiol levels in the pellet group were  $113 \pm 12$  pg/ml and remained relatively constant for 24 weeks. In contrast, estradiol levels in the patch group were  $52 \pm 11$  pg/ml at 1 week and then varied widely until 24 weeks, when the levels were  $89 \pm 26$  pg/ml. The mean estradiol/estrone ratio ranged between 1 and 2.5 in both groups but fluctuated widely in the patch group. Follicle-stimulating hormone was suppressed in both groups; however, the decrement in the pellet group was greater ( $p < 0.002$ ). There was a significant increase in high-density lipoprotein cholesterol and a decrease in total cholesterol/high-density lipoprotein cholesterol at 12 weeks with the pellet but only at 24 weeks with the patch. The urinary calcium/creatinine ratio was reduced more consistently with the pellet than with the patch. Hot flushes were eliminated in all subjects. (*AM J OBSTET GYNECOL* 1988;159:1540-6.)

**Key words:** Estradiol, postmenopausal women, estrogen replacement therapy

Although the oral route is the most common form of estrogen replacement therapy in postmenopausal women, parenteral estrogen replacement therapy offers several theoretic advantages. Perhaps the most important advantage of parenteral over oral estrogen replacement therapy is that the former route avoids the first-pass effect. There is evidence that the hepatic ef-

fects of oral estrogen replacement therapy may contribute to complications sometimes associated with oral estrogen replacement therapy, such as hypertension, intravascular clotting, and gallbladder disease.<sup>1-3</sup> Parenteral routes of estrogen replacement therapy may avoid these exaggerated hepatic actions and in addition may provide postmenopausal women with an alternative to oral estrogen replacement therapy.

Although several parenteral routes of estrogen replacement therapy are currently available, there is a paucity of data on estrogen levels achieved by these delivery systems and their effects on gonadotropins and metabolic parameters. The objective of this study was to compare the transdermal and subdermal routes of estrogen administration. These methods are considered the most available and practical routes of estrogen

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**Table I.** Percentage of subjects in the pellet and patch groups with serum E<sub>2</sub> concentrations <20 and 40 pg/ml

Time of sample	<20 pg/ml, % of subjects		<40 pg/ml, % of subjects	
	Pellet	Patch	Pellet	Patch
72 hrs	0	20	0	50
1 wk	0	0	0	50
2 wk	0	10	0	50
4 wk	0	0	0	70
8 wk	0	0	0	60
12 wk	0	30	0	40
16 wk	0	20	0	40
20 wk	0	10	0	20
24 wk	0	0	0	20

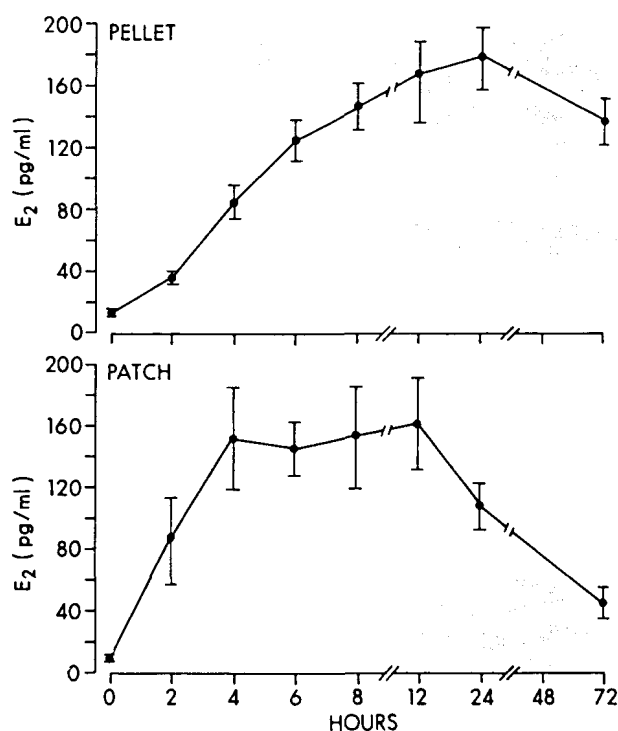
delivery and are generally preferred over intramuscular and vaginal routes. Specifically, we studied the constancy of estrogen delivery and the estrogen effect on follicle-stimulating hormone (FSH), lipids, and the calcium calcium/creatinine ratio.

**Methods**

The study group consisted of 20 women between 40 and 65 years of age. All the women had undergone total abdominal hysterectomy, and 12 had also undergone bilateral salpingo-oophorectomy. All the subjects were considered postmenopausal on the basis of serum estradiol (E<sub>2</sub>) levels <20 pg/ml and serum FSH levels >40 mIU/ml. The mean (±SD) weights of the subjects in the pellet and patch groups were 148 ± 13 and 136 ± 13 pounds, respectively. Each subject was within 20% of ideal body weight; however, the subjects' diets were not controlled. All subjects were nonsmokers.

The study subjects were randomized according to a table of random numbers. They received either a transdermal E<sub>2</sub> system (Estraderm, CIBA-GEIGY Pharmaceutical Co., Summit, N.J.), which was 4 cm in diameter, contained 8 mg of E<sub>2</sub>, and delivered 0.1 mg of E<sub>2</sub>/day,<sup>4</sup> or a subdermal E<sub>2</sub> system (Progyon Associates, Rosemont, Ill.) consisting of two 25 mg crystalline E<sub>2</sub> pellets. These systems will be subsequently referred to as patch and pellet, respectively. Ten subjects were in each study group. Pellets were inserted subdermally with a trocar through a small skin incision in the lower abdominal area. The patch was attached to the anterior lower abdominal wall and was changed twice weekly at 3- and 4-day intervals according to the manufacturer's directions. Each subject in the patch group was instructed to return the used patch before receipt of a new one. Ninety-five percent of the patches were returned.

Both blood and urine samples were obtained from the subjects. Blood was sampled before treatment and



**Fig. 1.** A 72-hour profile of mean (±SE) serum E<sub>2</sub> levels before and during subdermal (pellet) and transdermal (patch) E<sub>2</sub> treatment.

2, 4, 6, 8, 12, 24, and 72 hours and 1, 2, 4, 8, 12, 16, 20, and 24 weeks after treatment was initiated. After the first 72 hours, blood sampling occurred between 8:00 and 10:00 AM in all patients. In patients receiving the patch, blood was obtained before the patch was changed on specified days. Pretreatment and 12- and 24-week specimens were taken after a 12-hour fast. The blood was allowed to clot at 4° C for 1 hour and after centrifugation, the separated serum was stored at -20° C until analyzed. Urine samples were obtained before treatment and 12 and 24 weeks after treatment started after a 12-hour fast. The subjects were required first to void and then to drink 250 ml of distilled water 2 hours before urine collection.

Estradiol, estrone (E<sub>1</sub>), FSH, and lipids were measured in the serum samples, and the calcium/creatinine ratio was measured in each urine specimen. E<sub>2</sub> was quantitated, which followed extraction with ethyl acetate:hexane (3:2), by means of an iodinated E<sub>2</sub> radioimmunoassay kit from Pantex (Santa Monica, Calif.). The lowest E<sub>2</sub> concentration that could be measured reliably was 8 pg/ml. Accuracy of the E<sub>2</sub> assay was assessed in a recovery experiment in which a known amount of E<sub>2</sub>, which ranged from 25 to 200 pg, was added to individual 1 ml aliquots of serum in duplicate. Linear regression analysis of the E<sub>2</sub> concentration measured (y) versus the E<sub>2</sub> concentration added (x) yielded the following equation and correlation coefficient:  $y = 1.15 \times + 16.2, r = 0.998$ . Assay precision was de-

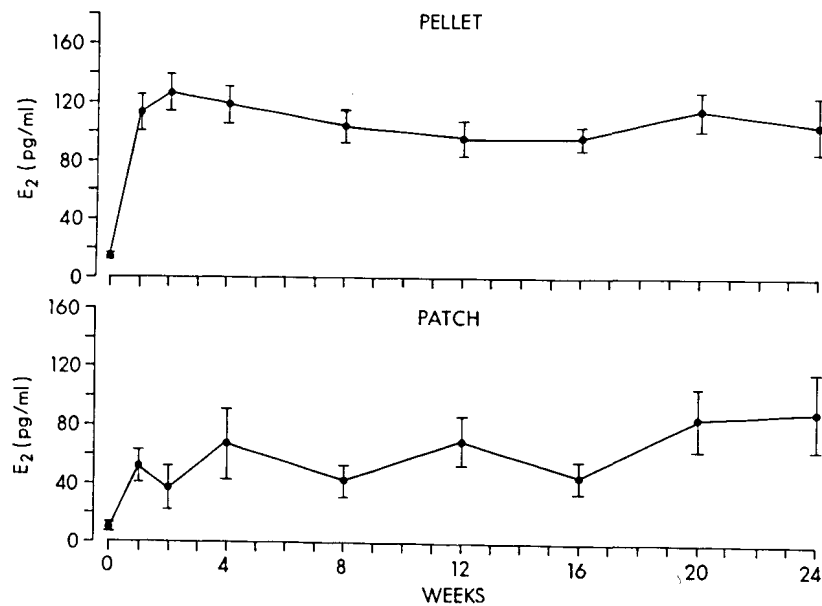


Fig. 2. Mean ( $\pm$ SE) serum E<sub>2</sub> levels before and during 1 to 24 weeks of subdermal (pellet) and transdermal (patch) E<sub>2</sub> treatment.

Table II. Percentage of subjects in the pellet and patch groups with serum E<sub>2</sub> concentrations >150 and 200 pg/ml

Time of sample	>150 pg/ml, % of subjects		>200 pg/ml, % of subjects	
	Pellet	Patch	Pellet	Patch
72 hrs	40	0	10	0
1 wk	10	0	0	0
2 wk	20	0	0	0
4 wk	30	20	0	10
8 wk	10	0	0	0
12 wk	10	10	0	0
16 wk	0	0	0	0
20 wk	10	10	0	0
24 wk	10	20	0	0

terminated at pooled serum E<sub>2</sub> concentrations of 52 pg/ml (low pool) and 119 pg/ml (high pool). The intraassay coefficients of variation ( $n = 6$ ) were 9.2% and 10.9%, and the interassay coefficients of variation ( $n = 28$ ) were 17.5% and 9.1% for the low and high pools, respectively. The E<sub>2</sub> antiserum cross-reacted 0.36% with E<sub>1</sub>. E<sub>1</sub> was measured by radioimmunoassay after diethyl ether extraction and celite column chromatography as described previously.<sup>4</sup> FSH was assayed by means of a double-antibody <sup>125</sup>I-FSH radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles, Calif.) in which the calibrators contained 0 to 100 mIU/ml of FSH in World Health Organization second international reference preparation—human menopausal gonadotropin. The lipid profiles and calcium/creatinine ratios were determined at SmithKline Bio-Science Laboratories (Van Nuys, Calif.). Each lipid

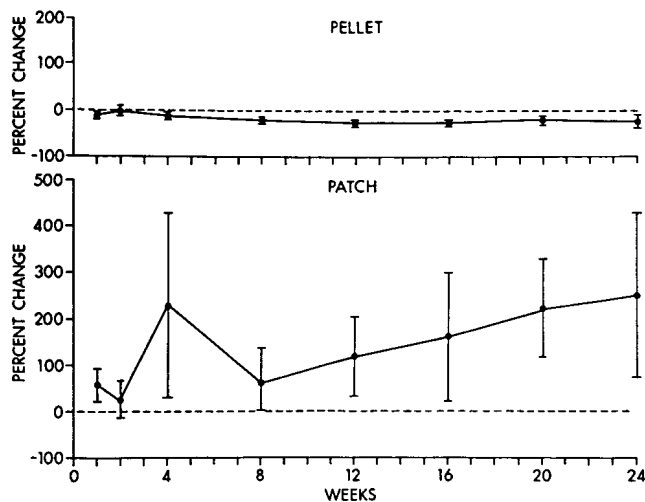
profile consisted of total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and total cholesterol/high-density lipoprotein cholesterol ratio. Total cholesterol and triglycerides were measured on an Olympus high-speed clinical analyzer with the use of enzymatic and spectrophotometric methods. High-density lipoprotein cholesterol was quantitated spectrophotometrically on an Abbott VP analyzer after phosphotungstic-magnesium chloride precipitation and centrifugation. Low-density lipoprotein cholesterol was calculated as described by Friedwald et al.<sup>5</sup> Urinary calcium and creatinine were measured by arsenazo dye and modified Jaffe reaction methods, respectively, and the calcium/creatinine ratio was then calculated.

Although not the primary focus of this study, subjects recorded symptoms weekly. From these diary cards, changes in vasomotor symptoms and reports of adverse effects were monitored.

Longitudinal data were analyzed by the nonparametric one-way analysis of variance (Friedman) for significance among the time variates. To determine the significance of difference between the baseline value and the values at different time intervals, the Wilcoxon matched-pairs sign ranks statistic was used. Differences between the two treatment groups were analyzed by the Mann-Whitney U test.

## Results

A 72-hour profile of serum E<sub>2</sub> was obtained and is shown in Fig. 1. In the pellet group, E<sub>2</sub> increased steadily during the first 24 hours after treatment and reached a mean E<sub>2</sub> concentration of 179 pg/ml at 24 hours. Peak levels were reached between 24 and 72

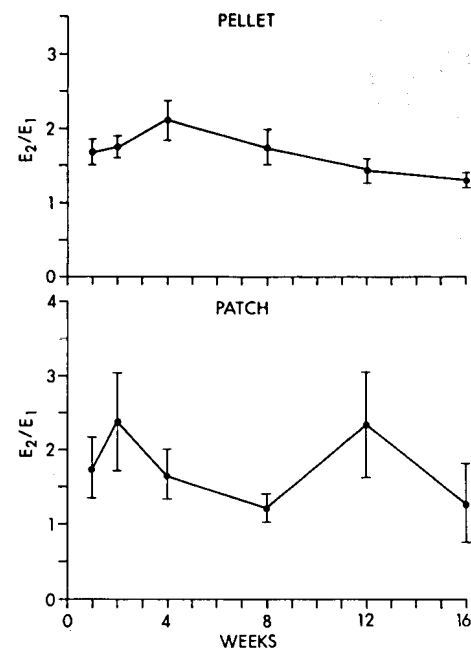


**Fig. 3.** Variation in serum E<sub>2</sub> levels during 1 to 24 weeks of subdermal (pellet) and transdermal (patch) E<sub>2</sub> treatment. Values at each time interval represent means ( $\pm$ SE) of each woman's E<sub>2</sub> level expressed as percentage change from the mean E<sub>2</sub> concentration at 72 hours.

hours, and the mean E<sub>2</sub> concentration at 72 hours was 139 pg/ml. In the patch group E<sub>2</sub> levels increased rapidly and reached a mean concentration of 152 pg/ml 4 hours after treatment. This level remained relatively constant during the next 8 hours but fell to a mean level of 46 pg/ml at 72 hours. In one subject in the patch group, the serum E<sub>2</sub> concentration was measured 48 hours after treatment (data not shown). The E<sub>2</sub> value at this time was approximately 40% higher than the corresponding 72-hour E<sub>2</sub> value.

The mean serum E<sub>2</sub> levels at different intervals from 1 to 24 weeks in the pellet and patch groups are depicted in Fig. 2. One week after treatment began, the E<sub>2</sub> concentration in the pellet group averaged 113 pg/ml. This level did not vary significantly during the rest of the study period. Furthermore, in two of the subjects in the pellet group, serum E<sub>2</sub> concentrations were measured weekly beyond 24 weeks (data not shown). In each subject the E<sub>2</sub> value at 32 weeks was not significantly different from the corresponding value at 24 weeks. In contrast, mean E<sub>2</sub> concentrations in the patch group varied widely during the study. The E<sub>2</sub> level at 1 week was 46 pg/ml, and this value was approximately doubled at 24 weeks. During this interval, the E<sub>2</sub> levels fell below or near 40 pg/ml at three different times (2, 8, and 16 weeks).

Variation in E<sub>2</sub> levels between the subjects in each treatment group was examined by expressing the mean E<sub>2</sub> levels at the different time intervals from 1 to 24 weeks as a percentage change from the mean E<sub>2</sub> concentration at 72 hours in each group (Fig. 3). In the patch group the mean percentage change ranged from approximately 25% to 225%. In comparison, the percentage change of mean E<sub>2</sub> levels in the pellet group



**Fig. 4.** Mean ( $\pm$ SE) serum estradiol E<sub>2</sub>/E<sub>1</sub> ratios during 1 to 16 weeks of subdermal (pellet) and transdermal (patch) E<sub>2</sub> treatment.

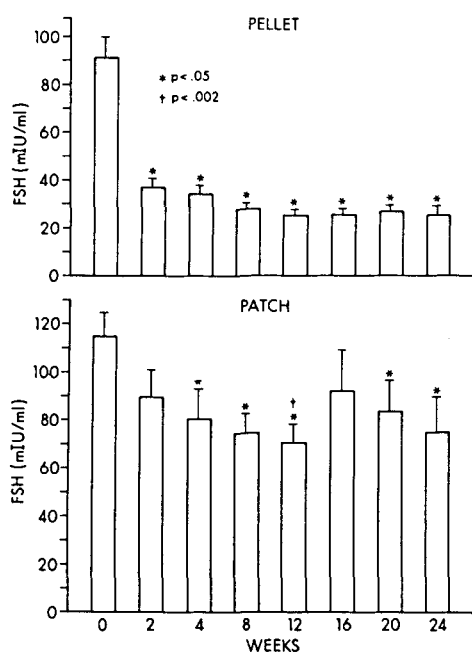
was small and remained relatively constant throughout the study.

Table I shows the percentage of study subjects with E<sub>2</sub> values <20 and 40 pg/ml. In the pellet group no subjects had E<sub>2</sub> levels <40 pg/ml. However, in the patch group 10% to 30% of the subjects had values <20 pg/ml at five different time intervals, and 20% to 70% had E<sub>2</sub> concentrations <40 pg/ml at all time intervals.

We also assessed the percentage of study subjects with E<sub>2</sub> values >150 and 200 pg/ml (Table II). Only a small number of subjects in the patch group had values >150 pg/ml, whereas 10% to 40% of the subjects in the pellet group exceeded this concentration at every time interval except one. However, only one subject in each treatment group exceeded E<sub>2</sub> concentrations >200 pg/ml.

Serum E<sub>1</sub> concentrations in the pellet and patch groups were compared over a 16-week period (data not depicted). In the pellet group, E<sub>1</sub> levels averaged 83 pg/ml after 1 week of treatment, and this level was maintained with little fluctuation. In the patch group the mean E<sub>1</sub> level at 1 week of the study was 32 pg/ml, and this value increased gradually during the study until the sixteenth week, at which time the level had doubled. The mean E<sub>2</sub>/E<sub>1</sub> ratio was calculated for the different time intervals from 1 to 16 weeks in each treatment group and ranged between 1 and 2.5 (Fig. 4). The ratio was relatively constant in the pellet group when compared with that of the patch group.

Mean serum FSH levels measured at different time intervals in the two treatment groups are shown in Fig. 5. In the pellet group FSH was significantly ( $p < 0.05$ )

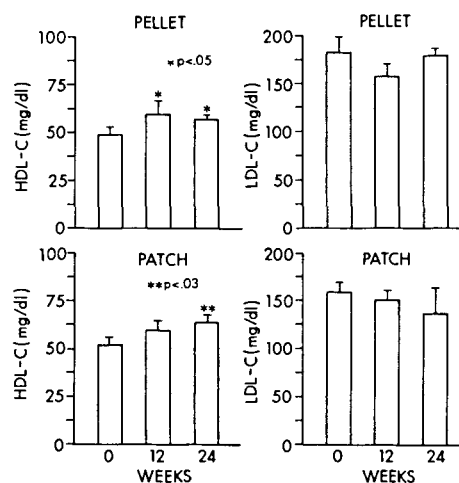


**Fig. 5.** Mean ( $\pm$ SE) serum FSH levels before and during 1 to 24 weeks of subdermal (pellet) and transdermal (patch)  $E_2$  treatment. The significance of difference in the comparison of FSH values at different time intervals with the baseline value is represented as  $*p < 0.05$ . The significance of difference between the two treatment groups is represented as  $\dagger p < 0.002$ .

suppressed from baseline values at every time interval, whereas in the patch group there was a significant decrease in FSH at 4, 8, 12, 20, and 24 weeks. The greatest suppression of FSH in both groups was at 12 weeks. Comparison of the percentage change from baseline between the two groups at 12 weeks showed a significantly greater ( $p < 0.002$ ) change in the pellet group.

Total cholesterol and triglycerides (data not depicted) did not change significantly in either treatment group. In the pellet group, high-density lipoprotein cholesterol increased significantly ( $p < 0.05$ ) from baseline at 12 and 24 weeks of the study, whereas in the patch group, high-density lipoprotein cholesterol also increased but was significantly greater ( $p < 0.03$ ) from baseline only at 24 weeks (Fig. 6). There was no significant difference from baseline in low-density lipoprotein cholesterol levels in either treatment group (Fig. 6). Comparison of the total cholesterol/high-density lipoprotein cholesterol ratios (Fig. 7) showed a significant ( $p < 0.01$ ) decrease from baseline at 12 and 24 weeks in the pellet group. In the patch group the ratios decreased from baseline at both time intervals but the difference was significant ( $p < 0.03$ ) only at the 24-week interval.

A reduction in urinary calcium/creatinine ratios (Fig. 8) from baseline occurred at both 12 and 24 weeks in



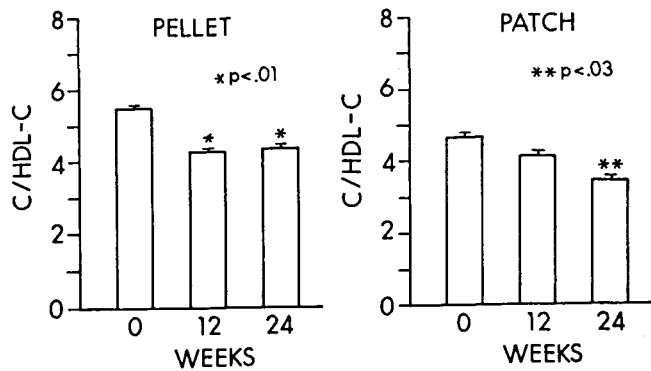
**Fig. 6.** Mean ( $\pm$ SE) serum high-density lipoprotein-cholesterol (HDL-C) levels before and during 12 and 24 weeks of subdermal (pellet) and transdermal (patch)  $E_2$  treatment. The significance of difference in the comparison of HDL-C values at 12 and 24 weeks with the baseline value is represented as  $*p < 0.05$  and  $**p < 0.03$ .

the pellet and patch groups. However, these reductions were significant ( $p < 0.01$ ) only in the pellet group.

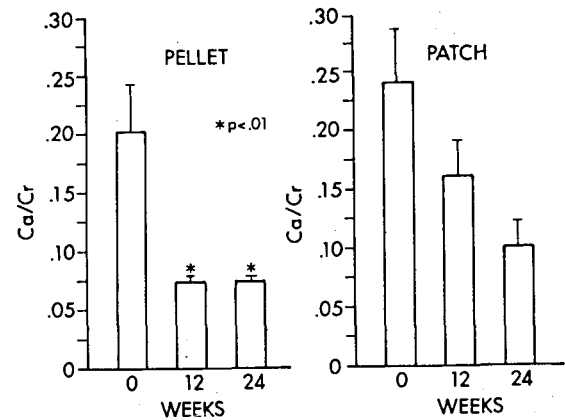
All subjects in our study had elimination of hot flashes; however, most subjects complained about local reactions caused by the  $E_2$  delivery systems. In the pellet group seven subjects complained of breast tenderness, especially around the areolar area. Two of the subjects had moderate to severe reactions and the rest had mild reactions. In the patch group, one subject complained about moderate to severe breast tenderness, and four other subjects had mild reactions. The duration of the complaints ranged from 8 to 24 weeks. None of the subjects in the pellet group complained of problems at the incision site. In the patch group, nine patients had a transient local skin reaction, and this effect persisted for a longer time in one subject, who also experienced some skin discoloration.

### Comment

In this study we compared subdermal and transdermal routes of estrogen administration. It has been previously shown that the subdermal  $E_2$  pellet offers many practical and theoretic advantages over other forms of estrogen replacement therapy.<sup>6,7</sup> We reported that a single 25 mg  $E_2$  subdermal pellet gives serum  $E_2$  concentrations in the range of 40 to 70 pg/ml over a 6-month period. To achieve higher serum  $E_2$  levels in the present study, we administered two 25 mg pellets subdermally in each subject in the pellet group. The mean  $E_2$  levels attained in these subjects ranged between 95 and 126 pg/ml (Fig. 2). The patch group



**Fig. 7.** Mean ( $\pm$ SE) serum total cholesterol (C)/high-density lipoprotein cholesterol (HDL-C) ratio before and during 12 and 24 weeks of subdermal (pellet) and transdermal (patch) E<sub>2</sub> treatment. The significance of difference in the comparison of the C/HDL-C ratios at 12 and 24 weeks with the baseline value is represented as \* $p < 0.01$  and \*\* $p < 0.03$ .



**Fig. 8.** Mean ( $\pm$ SE) urinary calcium (Ca)/creatinine (Cr) ratio before and during 12 and 24 weeks of subdermal (pellet) and transdermal (patch) E<sub>2</sub> treatment. The significance of difference in the comparison of the urinary Ca/Cr ratios at 12 and 24 weeks with the baseline value is represented as \* $p < 0.01$ .

used the 0.1 mg E<sub>2</sub> transdermal system. Although patches are available commercially in two doses, 0.05 and 0.1 mg of E<sub>2</sub>, the former dose results in E<sub>2</sub> levels that are closer to the single 25 mg pellet.<sup>6,8</sup>

Our data clearly show that the pellet provides a more reproducible estrogen delivery system than the patch. The serum E<sub>2</sub> levels of each subject in the pellet group were relatively constant throughout the study, whereas the E<sub>2</sub> values for each subject in the patch group varied widely. The fluctuation in E<sub>2</sub> levels in the patch group may be related to inherent properties of the patch or compliance issues. One inherent property of the patch is that its release of E<sub>2</sub> gives rise to a peak and nadir of E<sub>2</sub> levels over a 72-hour period (Fig. 1), which is similar to that observed during a 24-hour period after oral ingestion of an E<sub>2</sub> preparation. Furthermore, lack of patient compliance in following the manufacturer's directions in using the patch can result in altered profiles of E<sub>2</sub> levels such as the ones observed in this study (Figs. 2 and 3). Although the subjects in the present study were encouraged to comply with the experimental protocol, our data suggest that there could have been a lack of compliance by subjects in the patch group.

Suppression of serum FSH levels was observed in both the pellet and patch groups. However, the FSH decrement was greater in the pellet group, presumably because of the higher E<sub>2</sub> concentrations and less fluctuations of these levels in this group. The FSH values in the pellet group were lower than the values obtained in our previous study in which a single E<sub>2</sub> pellet was implanted subdermally in women who underwent hysterectomy and bilateral salpingo-oophorectomy.<sup>6</sup> The lower FSH levels were expected since higher serum E<sub>2</sub> concentrations were attained in the present study. With respect to the FSH levels in the patch group, our results

are in agreement with those of other investigators,<sup>8-11</sup> albeit the degree of suppression varied with the E<sub>2</sub> dose of the patch.

Although total cholesterol and triglycerides did not change significantly in either treatment group, there was a significant increase in high-density lipoprotein cholesterol and a decrease in the total cholesterol/high-density lipoprotein cholesterol ratio by 12 weeks of the study in the pellet group but only at 24 weeks in the patch group. Very few studies have found changes in high-density lipoprotein cholesterol with parenteral forms of estrogen. The estrogen effect on lipoproteins may occur only after sufficient estrogen is delivered over a prolonged time, such as 6 months. Although patients wearing a patch had fluctuating levels of E<sub>2</sub>, which were extremely low at times, the finding of an increase in high-density lipoprotein cholesterol at 6 months is novel and important. Nevertheless, larger numbers of subjects and more sophisticated lipoprotein determinations are needed to confirm these data.

Although there was a reduction in the fasting urinary calcium/creatinine ratio at 12 and 24 weeks in the patch group, our data show a more consistent reduction of this ratio in the pellet group. However, the calcium/creatinine ratio is a relatively crude marker of bone turnover and merely provides a guide for the effects of estrogen on bone.

All subjects in our study had elimination of hot flashes. Although differences in the frequency and severity of the flushes were not analyzed, the benefits of the pellet and patch with respect to suppression of hot flashes appear to be comparable.

Our data show that over 24 weeks, the pellet offers a more reproducible estrogen delivery and greater es-

trogen effect. These advantages of the pellet over the patch may be related to inherent properties of the patch or issues of patient compliance. In our study group dermatologic complaints were fairly common. However, there was no difference in serum  $E_2$  levels between patients having and not having such complaints.

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