

ENDOCRINE AND CLINICAL EFFECTS OF ESTRADIOL AND TESTOSTERONE PELLETS USED IN LONG-TERM REPLACEMENT THERAPY

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Abstract

Kapetanakis E, Dmowski WP, Auletta F, Scommegna A (Michael Reese Hospital and Medical Center, University of Chicago Pritzker School of Medicine, Chicago, IL, USA). Endocrine and clinical effects of estradiol and testosterone pellets used in long-term replacement therapy.

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Ten women with estrogen deficiency symptoms because of premature menopause [3], gonadal dysgenesis [3], or surgical menopause [4] received subcutaneous implants consisting of 25–75 mg estradiol (E_2) with or without 75 mg testosterone (T). All had elevated plasma FSH, and LH, and low E_2 prior to treatment. Plasma levels of FSH, LH, E_2 , T and estrone (E_1) were measured by specific radioimmunoassay techniques prior to treatment, three times a week for the first week and once a week for up to 76 weeks after implantation.

Mean plasma E_2 levels rose abruptly and reached a maximum of 190 ± 35 pg/ml within 2 weeks. They fluctuated around 150 pg/ml for 46 weeks, then gradually declined, but remained above pretreatment values for more than 68 weeks. Plasma E_1 increased to a lesser extent resulting in $E_2 : E_1$ ratio between 1 and 5. Elevated FSH and LH titers became suppressed within 4–6 weeks.

The lowest average E_2 increase occurred after 25 mg implant and was associated with

incomplete FSH and LH suppression. There were no differences in maximal E_2 levels reached after 50 mg or 75 mg implant, however, after 75 mg implant, E_2 levels appeared less variable and were sustained for a longer period of time, averaging 125 pg/ml for 70 weeks.

Plasma FSH and LH concentrations were suppressed below pretreatment levels in all patients. The degree of suppression was related to the dose of E_2 implanted and, therefore, to plasma E_2 levels. The FSH and LH suppression appeared more complete in women with gonadal dysgenesis than in those with premature or natural menopause.

Plasma T rose abruptly to a peak mean level of 2.5 ± 1.6 ng/ml within 2 weeks of implantation. A precipitous and steady decline with return to preimplantation titers between 17th and 18th week were then observed. The $E_2 : E_1$ ratio during the first 18 weeks after implantation was significantly higher in women who received E_2 implant alone than in those who received $E_2 + T$ implant. Clinically, all patients had symptomatic improvement within 24–48 hours. Regular withdrawal bleeding followed administration of oral progestogen for up to 76 weeks after implantation in six patients with intact uterus.

Key words: Endocrine; Estradiol and Testosterone; Estrogen deficiency symptoms; Pre-

mature menopause; Gonadal dysgenesis; Subcutaneous implants; Measured by radio-immunoassay techniques; Suppressed plasma FSH and LH concentrations; Oral progestogen

Introduction

Subcutaneous implantation of estrogen pellets to reverse or prevent clinical endocrinological or metabolic changes of ovarian failure is probably one of the oldest approaches to estrogen replacement therapy [4]. Pellets containing pure estradiol have been used by many investigators in the 1940s and '50s [5,6,11,14,23], then they became less popular when a variety of synthetic or natural but orally active estrogenic compounds entered the market. Estradiol pellets, however, are still considered to offer advantages over other methods of estrogen replacement [9]. Some investigators recommend that testosterone pellets be implanted in combination with estradiol to achieve anabolic effect, improve libido, correct fatigue and cure headache, symptoms reported by many women with ovarian failure [8-11].

Previous studies involving estradiol and testosterone pellets used predominantly clinical parameters to determine the duration and amount of the steroid released, and the effect of the pellets. The degree of absorption of the steroid was measured by subsequent recovery and weighing of the pellet [10,11]. Although several more recent studies [12,13,15,19,27] using radioimmunoassay techniques have provided new information on endocrinological effects of estradiol pellets, many questions still remain unanswered. Little is known, for instance, about absorption of the steroid from the pellet, variability in its plasma levels in relation to time and the number of pellets, effect of testosterone on estradiol:estrone ratio, and about the degree of gonadotropin suppression by the pellets in different disorders.

To answer these as well as other

questions, we have studied the effect of pellets containing either estradiol (E_2) or estradiol in combination with testosterone (T) on plasma levels of FSH, LH, estrone, estradiol and testosterone in ten women with various types of ovarian failure.

Materials and methods

The subjects in this study were ten women with estrogen deficiency symptoms (Table I). Three patients had premature menopause, three gonadal dysgenesis, and four had total abdominal hysterectomy and bilateral salpingo-oophorectomy for a benign disease. The youngest patient was 19, a total of six patients were less than 35 and the oldest patient was 58. All with the exception of two (patients J.H. and J.E., Table I) received previously some form of estrogen replacement but no treatment for at least 6 weeks prior to entering this study. The two patients mentioned entered the study shortly after surgery and did not receive previous estrogen replacement. All ten patients had low plasma estradiol, elevated plasma FSH and LH, amenorrhea, and a variety of estrogen deficiency symptoms listed in Table I.

Each pellet used for subcutaneous implantation contained either 25 mg of crystalline estradiol (Progynon[®], Schering Corporation) or 75 mg of testosterone (Oreton[®], Schering Corporation). Between one and three estradiol pellets, with or without testosterone pellet, were implanted in the subcutaneous tissue of the lower abdomen (Table I). Implantations were performed after local infiltration of the skin with 1-2 ml of xylocaine, using aseptic technique and Kearn's pellet implanter. The site of implantation was covered with a bandaid and no sutures were required.

Blood samples for FSH, LH, estradiol, estrone and testosterone were obtained in the A.M., three times a week for the first week, and once a week for up to 76 weeks

after implantation. Plasma FSH and LH levels were determined using BIO-RIA kits (Montreal, Quebec, Canada) according to the double antibody method of Midgley

Table I. Clinical data on 10 patients treated with subcutaneous pellet implants.

Pt Inits	Age	Parity	Diagnosis	Symptoms	Composi- tion of implant	Clinical effect	Return of symptoms
H.R.	41	1001	Premature meno- pause at age 28	Secondary amenor- rhea, hot flushes, other menopausal symptoms	75 mg E ₂ + 75 mg T	Symptom free within 48 h, regular WTB	Asymptomatic for 70 weeks of observation
H.E.	32	2022	Premature meno- pause at age 30	Secondary amenor- rhea, hot flushes, other menopausal symptoms	75 mg E ₂ + 75 mg T	Symptom free within 48 h, regular WTB	Asymptomatic for 54 weeks of observation
L.C.	30	2011	Premature meno- pause at age 28	Secondary amenor- rhea, hot flushes, other menopausal symptoms	75 mg E ₂ + 75 mg T	Symptom free within 48 h, regular WTB	Asymptomatic for 80 weeks of observation, 75 mg T
G.E.	27	0000	Gonadal dysgene- sis (karyotype 45,X0)	Primary amenorrhea, headaches, fatigue	75 mg E ₂ + 75 mg T	Symptom free within 48 h, regular WTB	Asymptomatic for 52 weeks of observation
B.G.	19	0000	Gonadal Dysgene- sis (karyotype 46, XX)	Primary amenorrhea, fatigue, tiredness	75 mg E ₂ + 75 mg T	Symptom free within 1 week, regular WTB	Return of fatigue, tiredness 16 weeks after treatment
M.E.	29	0000	Gonadal Dysgene- sis (karyotype 46, XX)	Primary amenorrhea	50 mg E ₂	Regular WTB	Asymptomatic for 45 weeks of observation
M.S.	26	0000	TAH, BSO at age 23	Hot flushes, weak- ness, loss of libido	50 mg E ₂ + 75 mg T	Symptom free within 48 h	Return of symptoms 24 weeks after treatment
J.H.	41	2002	TAH, BSO at age 41	Hot flushes and other menopausal symptoms	50 mg E ₂	Symptom free within 48 h	Asymptomatic for 62 weeks of observation
V.E.	58	0000	TAH, BSO at age 47	Hot flushes, weak- ness, other meno- pausal symptoms	25 mg E ₂ + 75 mg T	Symptom free within 48 h	Return of symptoms 12 weeks after treatment
					50 mg E ₂ + 75 mg T	Symptom free within 48 h	Return of symptoms 32 weeks after treatment
J.E.	46	2002	TAH, BSO at age 48	Hot flushes, other menopausal symptoms	50 mg E ₂	Symptom free within 48 h	Asymptomatic for 63 weeks of observation

TAH, BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy.

E₂ = estradiol.

T = testosterone.

WTB = withdrawal bleeding after administration of progestogen.

[17,18]. In our laboratory, the FSH assay sensitivity averaged 0.08 mIU (LER-907, Second International Reference Preparation (Second IRP)) when assaying 100 μ l of plasma. The interassay ($n = 20$) and intra-assay ($n = 34$) coefficients of variation were 12.3% and 6.4%, respectively. The LH assay sensitivity averaged 0.16 mIU/100 μ l (LER-907, Second IRP). The interassay ($n = 20$) and intra-assay ($n = 34$) coefficients of variation were 14.1% and 8.1%, respectively. Each unknown was run in duplicate using 50 μ l and 100 μ l of plasma.

Plasma estrone, estradiol and testosterone were assayed by the specific radioimmunoassay procedures as previously reported [1-3].

Six patients with uterus *in situ* received progestogen orally at monthly intervals (medroxyprogesterone acetate, 10-mg tablets,

one tablet twice a day for 5 days) to induce a withdrawal bleeding.

Results

Plasma concentrations of FSH, LH, estradiol and estrone following subcutaneous implantation of one estradiol and one testosterone pellet are demonstrated in Fig. 1. Plasma estradiol reached a maximum of 210 pg/ml during the first week, then fluctuated at much lower level, around 70 pg/ml, for the following 15 weeks. Plasma estrone also increased as compared to pre-treatment values and its levels fluctuated close to those of estradiol. Plasma FSH concentrations decreased by about 50% 5 weeks after implantation of the pellets, then began to rise, reaching values higher than those before

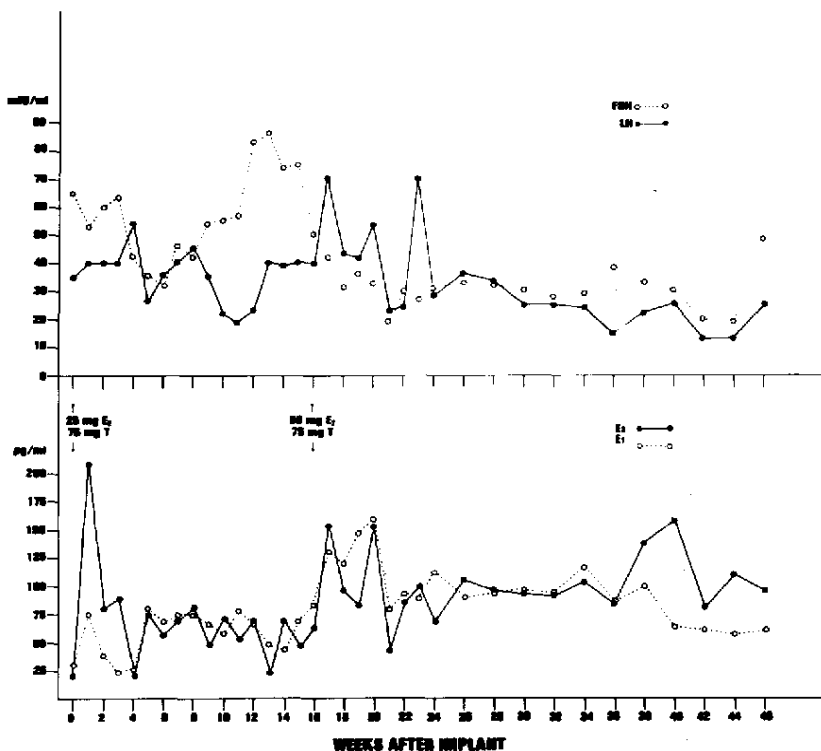


Fig. 1. Plasma FSH, LH, estradiol (E₂) and estrone (E₁) in patient V.E. following subcutaneous implant of 25 mg E₂ and 75 mg T, followed by another implant of 50 mg E₂ and 75 mg T.

treatment between the 12th and 16th week. There was no change observed in plasma LH concentrations. Clinically, the patient was symptom-free within 48 h after implantation but had a return of symptoms between the 12th and 16th week. Two E_2 and one T pellets were implanted 16 weeks after the initial implant. The patient became asymptomatic promptly and remained so for twice as long period of time (32 weeks). After the second implant, plasma estradiol reached higher levels fluctuating around 90 pg/ml for 30 weeks of observation. Plasma estrone concentrations seemed to correspond closely to those of estradiol. FSH and LH levels after the second pellet insertion became suppressed to values around 30 mIU/ml.

Three patients received an implant consisting of two E_2 pellets. Mean Plasma FSH, LH, estradiol and estrone concentrations in

these patients are demonstrated in Fig. 2. Plasma estradiol increased abruptly within the first week and reached the maximum of just under 200 pg/ml within 2 weeks after implantation. Subsequently, its levels fluctuated around 125 pg/ml for 50 weeks showing a gradual tendency to decline. However, even at 62 weeks after implantation, plasma estradiol was higher than prior to treatment. Plasma estrone was also increased but to a lesser extent. It remained in a relatively constant range between 40 and 75 pg/ml during the entire period of 62 weeks after implantation. Plasma FSH and LH became suppressed to less than 10 mIU/ml within 3–4 weeks after implantation. All three patients became symptom-free within 48 h and continued to be asymptomatic during the period of observation. One of three, patient M.E. with primary amenorrhea and gonadal

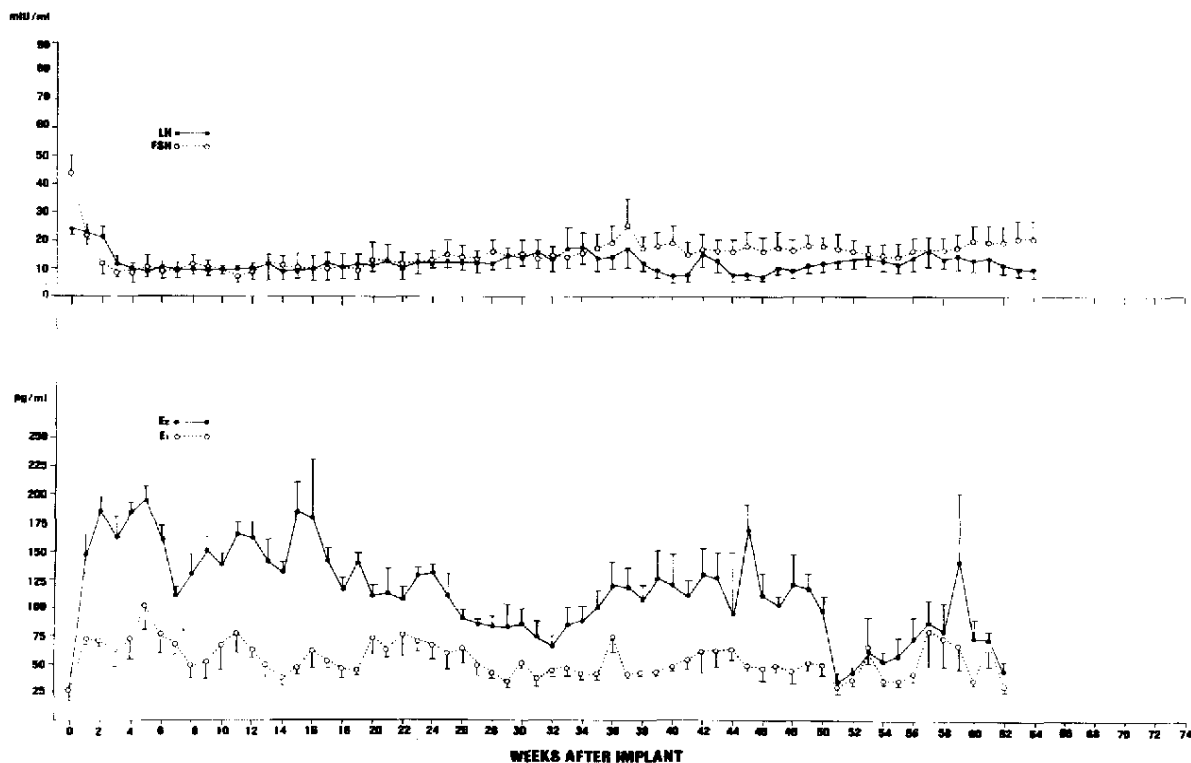


Fig. 2. Plasma FSH, LH, estradiol (E_2) and estrone (E_1) in three patients following subcutaneous implant of 50 mg E_2 (Mean \pm S.E.M.).

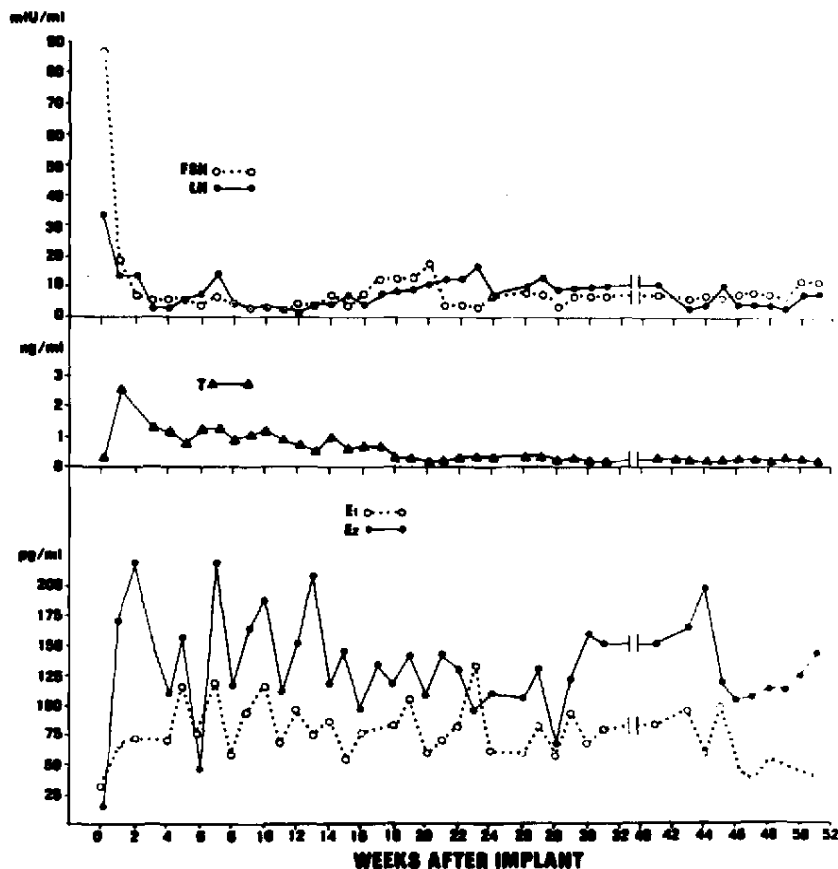


Fig. 3. Plasma FSH, LH, estradiol (E_2), estrone (E_1) and testosterone (T) in patient G.E. following subcutaneous implant of 75 mg E_2 and 75 mg T.

dysgenesis, had regular withdrawal bleeding after each monthly progestogen administration for 45 weeks of observation.

Five patients received a subcutaneous implant consisting of three E_2 and one T pellets. Plasma FSH, LH, estradiol, estrone and testosterone concentrations in one such patient with gonadal dysgenesis are demonstrated in Fig. 3. Plasma estradiol increased abruptly reaching a maximum of 225 pg/ml within 2 weeks after implantation. For the following 50 weeks of observation, plasma estradiol fluctuated around 130 pg/ml. Plasma estrone increased as compared with pretreatment values but remained persistently below plasma estradiol levels,

fluctuating around 80 pg/ml. Plasma testosterone showed an initial rise to 2.5 ng/ml within the first week after implantation, then declined to pretreatment values within 18 weeks. Plasma FSH and LH levels became suppressed during the first week of treatment and remained suppressed well below 20 mIU/ml during the entire period of observation. The patient became asymptomatic within 48 h after pellet implantation and remained symptom-free for 52 weeks of observation. She had regular monthly withdrawal bleeding after oral administration of progestogen.

Plasma FSH, LH, estradiol and estrone concentrations following subcutaneous implantation of three E_2 and one T pellets in

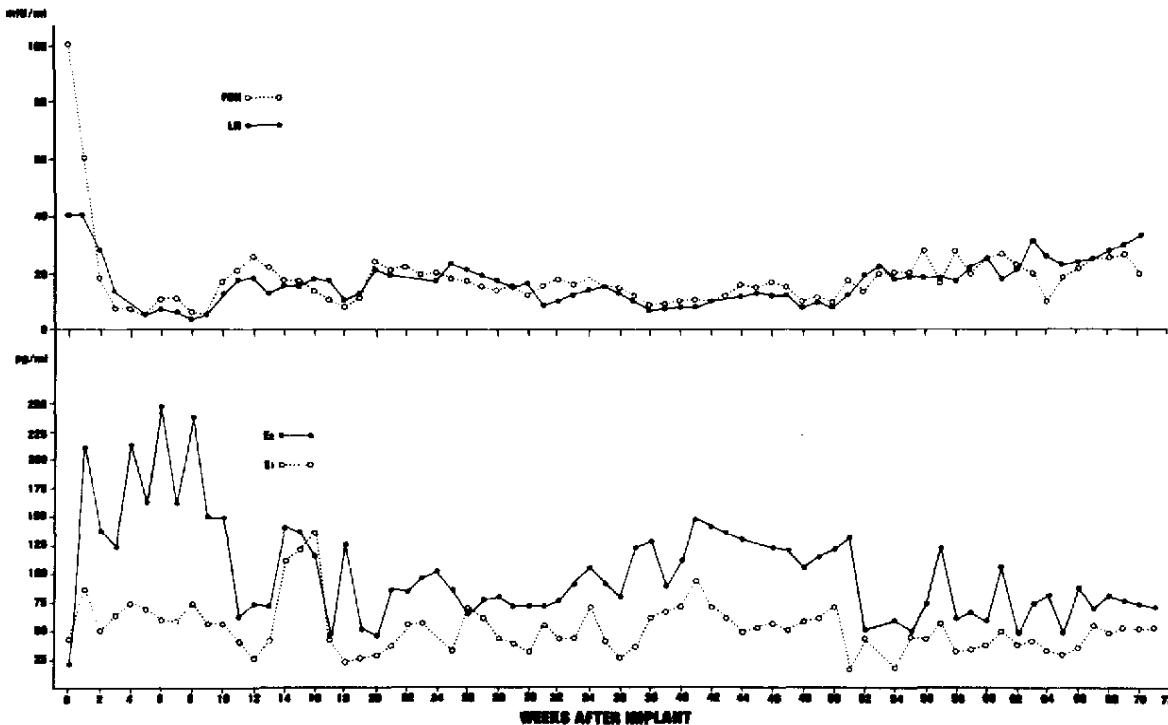


Fig. 4. Plasma FSH, LH, estradiol (E_2) and estrone (E_1) in patient H.R. following subcutaneous implant of 75 mg E_2 and 75 mg T.

patient H.R. with premature menopause are demonstrated in Fig. 4. Plasma estradiol reached close to the maximum level within the first week after implantation and remained elevated for 72 weeks of observation. Plasma estrone also increased but not to the same degree. Plasma FSH and LH became suppressed promptly ranging between 10 and 40 mIU/ml and remained below pre-treatment values for the entire period of observation. The patient had prompt symptomatic improvement after pellet implantation and remained asymptomatic having regular withdrawal menses for 72 weeks of observation.

A composite graph of mean \pm S.E.M. concentrations of FSH, LH, E_1 , and E_2 in all five patients who received subcutaneous implant of three E_2 and one T pellets is demonstrated in Fig. 5. The mean plasma estradiol levels

remained elevated for up to 70 weeks after implantation and were higher than mean plasma levels of estrone.

The ratio of estradiol to estrone was calculated separately for seven patients who received both estradiol and testosterone implants and for three patients who received estradiol implant alone (Fig. 6). For the first 18 weeks after implantation, this ratio was significantly different ($P < 0.001$) between both groups of patients. There was no difference between the ratios during the remaining period of observation.

Plasma testosterone levels were measured in all seven patients who received combined estradiol/testosterone implant. The mean \pm S.E.M. concentrations are demonstrated in Fig. 7. Plasma testosterone increased abruptly within 1 week and reached the maximum of 2.5 ng/ml 2 weeks after im-

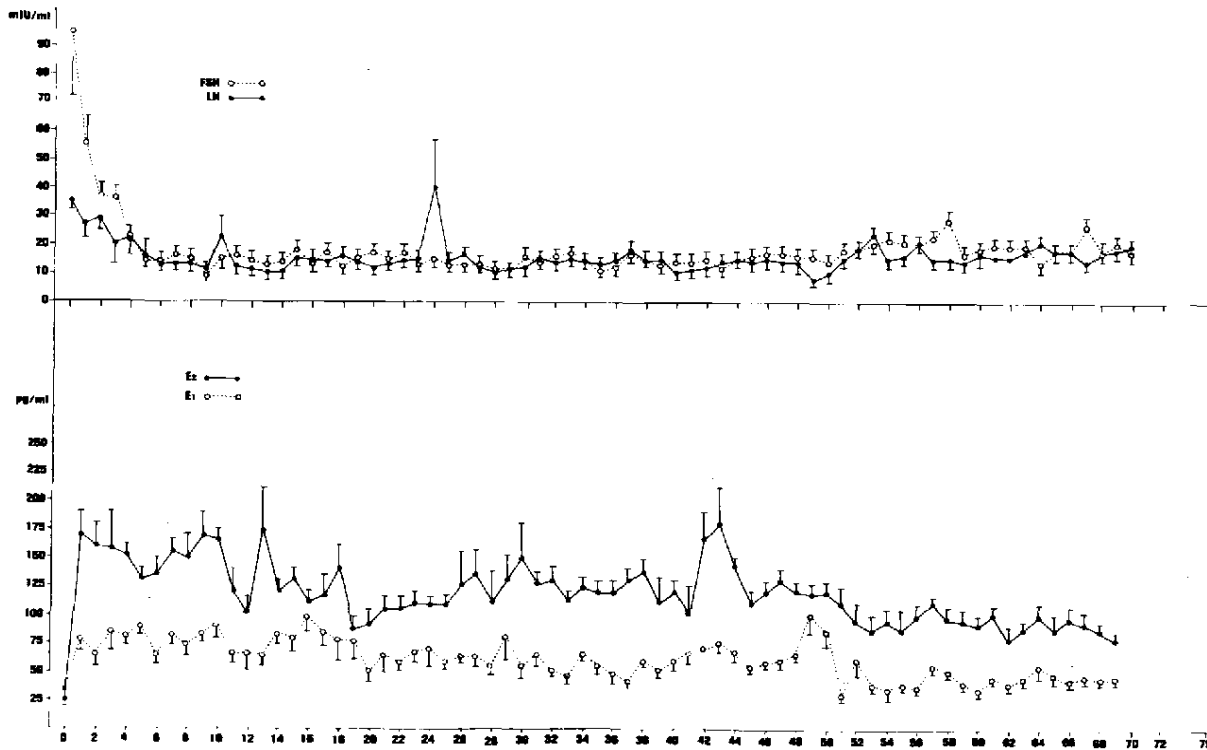


Fig. 5. Plasma FSH, LH, estradiol (E₂) and estrone (E₁) in five patients following subcutaneous implant of 75 mg E₂ and 75 mg T (Mean \pm S.E.M.).

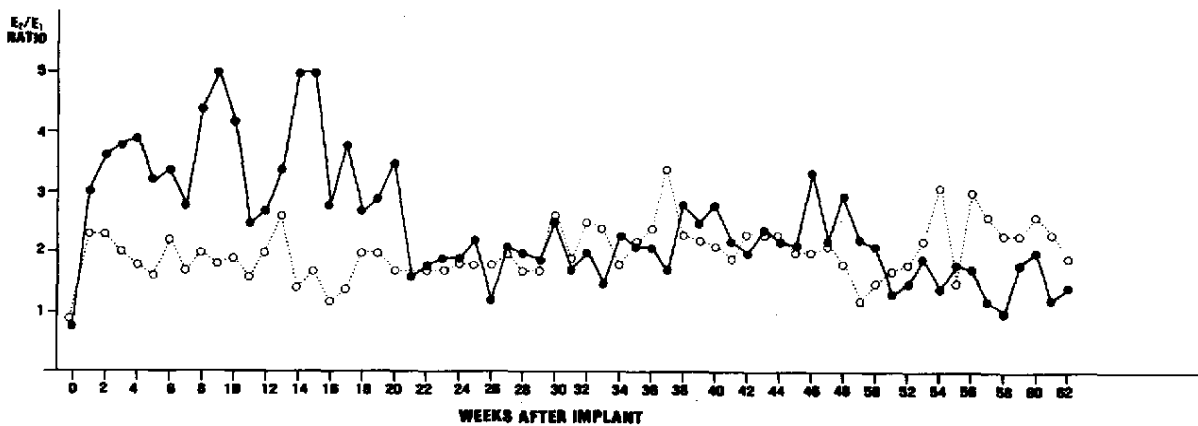


Fig. 6. Plasma estradiol (E₂) : estrone (E₁) ratio in three patients who received E₂ implant \bullet — \bullet and in seven patients who received E₂ and testosterone implant \circ --- \circ . The differences between both groups were statistically significant ($P < 0.001$) during the first 18 weeks of observation.

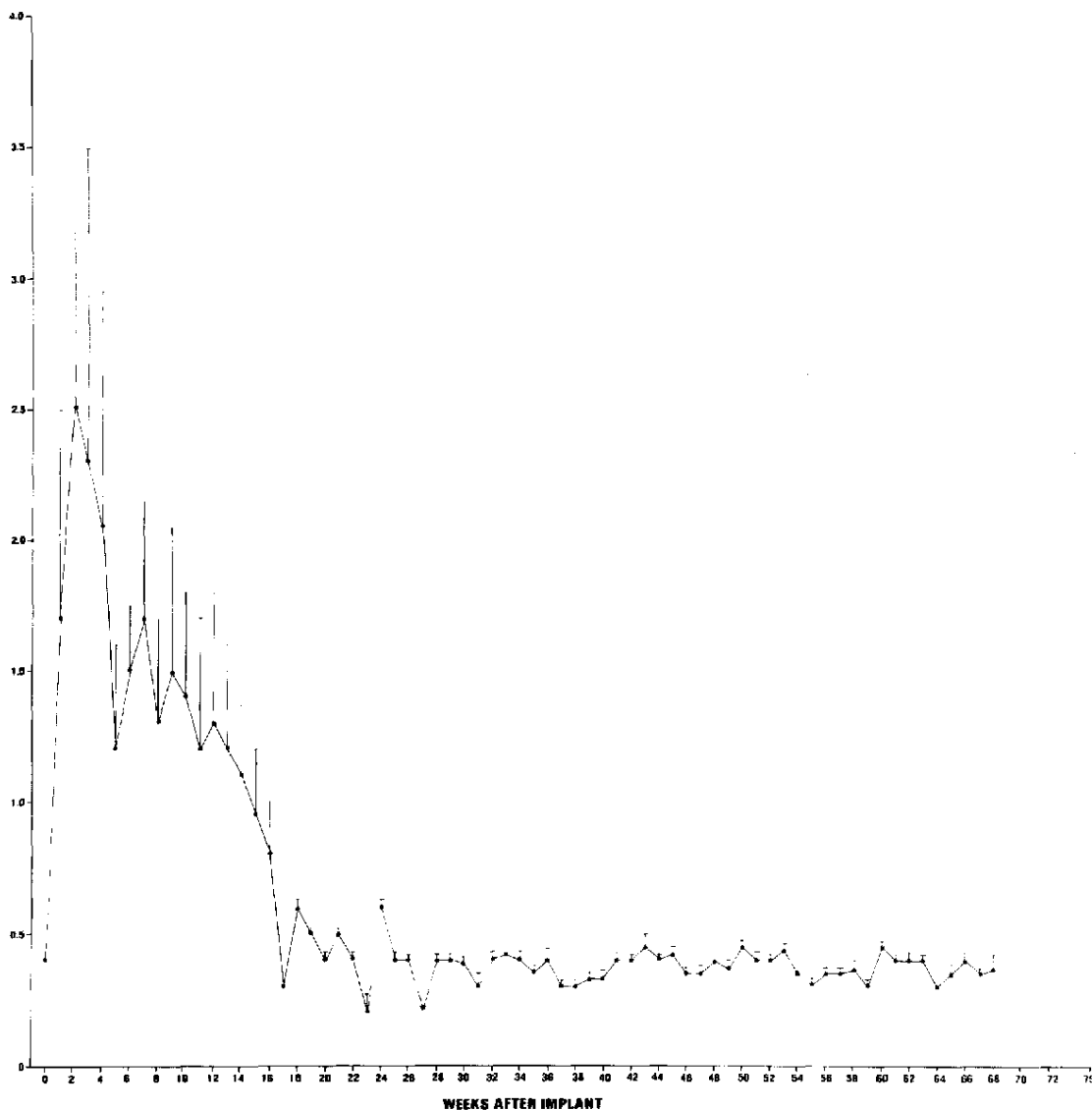


Fig. 7. Plasma testosterone (T) levels (ng/ml) in seven patients following subcutaneous implant of 75-mg T pellet (Mean \pm S.E.M.).

plantation. Subsequently, plasma testosterone declined precipitously, reaching pretreatment values 18 weeks after implantation.

Discussion

Estradiol pellets implanted subcutaneously

as a long-term estrogen replacement carry most of the associated benefits and risks of estrogen therapy. However, advantages of the pellets and the absence of some disadvantages of oral preparations have made such implants a preferred method of estrogen replacement for various investigators [9].

The estrogenic component of the pellet is estradiol, the main and the most active estrogen in the human female. Several reports indicate that the so-called "natural estrogens" have a more physiologic effect and do not induce undesirable metabolic side effects as compared with the synthetic, oral steroids [22,28–30]. Orally administered estrogens enter systemic circulation through the liver exerting pharmacological, dose related effects, on this organ [24]. Furthermore, oral estrogens including micronized 17 β -estradiol appear in the plasma predominantly as conjugates of estrone [31]. The physiologic ratio of estradiol to estrone characteristic for the reproductive age apparently cannot be achieved with orally administered preparations. It is likely that at least some of the adverse effects of estrogen replacement are associated with oral route of administration and with synthetic preparations.

Parentally administered estrogens do not change plasma levels of triglycerides [16], do not undergo as extensive conversion to estrone [20,21,25] and are conjugated less rapidly [26]. It has been demonstrated recently that following subdermal implantation of one 25-mg estradiol pellet there was no change in the binding capacity of serum corticosteroid and testosterone-estradiol binding globulins, no change in total cholesterol, triglycerides and low density lipoprotein-cholesterol levels, while high density lipoprotein-cholesterol increased significantly [15]. Serum estradiol concentration determined in that study reached the maximal value within 3 weeks after insertion, then declined slowly for a period of 6 months; at all times estradiol levels were above those of estrone resulting in the E₂ to E₁ ratio greater than one [15].

In our study, following a 25-mg estradiol implant, plasma estradiol concentrations achieved the maximal value within 2 weeks but then declined abruptly to pretreatment levels within 16 weeks after insertion.

It has been demonstrated by Nagamani *et*

al. [19] that after insertion of two estradiol pellets (50 mg) plasma concentrations of estradiol increase abruptly within the first week and remain elevated for as long as 14 weeks. Hunter *et al.* [13] reported elevated plasma estrogens for up to 24 weeks after implantation of 100-mg estradiol pellets. There have been no studies to determine if concentrations of estradiol in the plasma remain elevated beyond that period of time. Nevertheless, it has been a clinical practice to reimplant one to four estradiol pellets every 6 months [9].

As demonstrated by the results of this study, plasma estradiol concentrations remain elevated for 62 weeks or more after the insertion of two pellets (50 mg) and for 70 weeks or more after three pellets (75 mg). In women with intact uterus this indicates the probability of a continuous estrogenic stimulation of the endometrium for almost 1.5 years after implantation of the pellets. In our study, all six patients with intact uterus continued to withdraw monthly with progestogens for up to 76 weeks after insertion of the pellets. There was no irregular breakthrough bleeding in any of our patients.

In individual patients, pronounced week-to-week fluctuations in estradiol levels were observed, indicating a variable degree of absorption from the pellet, controlled most likely by local factors. Not surprisingly, the lowest average estradiol increase was noted in a patient who received the lowest dose, that is, 25 mg of estradiol implant. There was no difference in maximal plasma estradiol concentrations reached after the 50-mg or 75-mg implant. However, after the 75-mg implant, estradiol concentrations appeared less variable and more sustained. At the 62nd week after pellet insertion, plasma estradiol was in the range of 50 pg/ml after a 50-mg implant and was twice as high after the 75-mg implant. In one patient about 76 weeks after a 50-mg implant, plasma estradiol concentrations, although still higher than prior to pellet insertion, demonstrated a

sustained decline associated with the rise in FSH and LH indicating a decline in the pellet contents. At all times after insertion, plasma estradiol concentrations remained in the physiologic range for the menstrual cycle [7]. Plasma estrone levels also increased but to a lesser degree than those of estradiol and remained relatively constant during the entire period of observation.

Symptomatic improvements were observed in all patients within 24–48 h. It is interesting to note that the above was coincidental with the elevation of plasma estradiol values and that a drop in plasma FSH and LH levels occurred only later. This observation reported earlier by Nagamani *et al.* [19] indicates that vasomotor symptoms of the menopausal syndrome may be related more to the decreasing estrogen values than to the increase in gonadotropin levels. However, patient V.E. (Fig. 1) reported a return of menopausal symptoms 12 weeks after the first implant when estradiol was still elevated, but when plasma FSH was increased to pretreatment levels.

Although suppression of plasma FSH and LH below pre-treatment levels was observed in all ten patients in this study, it appeared that the degree of suppression was not the same in different disorders. In agreement with the earlier reports by Nagamani *et al.* [19], FSH and LH levels suppressed readily to or below 10 mIU/ml in patients with gonadal dysgenesis. In three patients with premature menopause as well as in one patient of the menopausal age, the FSH and LH suppression appeared less complete. Plasma FSH and LH levels in these patients, although suppressed significantly below the initial pretreatment values, remained between 10 and 30 mIU/ml. As could be expected, the completeness of FSH and LH suppression in our menopausal patient was directly related to the number of pellets implanted and to plasma estradiol concentrations.

Plasma testosterone levels rose abruptly after implantation and achieved a peak level 2 weeks later. Subsequently, a precipitous

and steady decline was observed with return to normal preimplantation values between the 17th and 18th week. No virilizing effects were observed, probably because of the short period of increase in testosterone concentrations and because of the concomitant increase in plasma estrogens. In three of our patients, the return of symptoms such as fatigue, tiredness, and loss of libido, 12–24 weeks after implantation could be attributed to absorption of the pellet and the decrease in plasma testosterone levels.

The $E_2 : E_1$ ratio in all patients during the entire course of treatment averaged 2.3 and remained consistently above 1. It is interesting, however, to compare the $E_2 : E_1$ ratio in three patients who received estradiol implant alone with the remaining seven patients who received both estradiol and testosterone implants. There was no significant difference in the ratios after the 18th week of treatment. For the first 18 weeks, however, the $E_2 : E_1$ ratio was significantly ($P < 0.001$) lower in patients who received both steroid implants. Higher plasma estrone levels after testosterone and estradiol implant than after estradiol implant alone along with plasma disappearance curve of testosterone during the initial 18 weeks of treatment, indicate that estrone originating from testosterone might have been responsible for the change in $E_2 : E_1$ ratio.

In conclusion, crystalline estradiol pellets implanted subdermally are absorbed into the peripheral circulation over a prolonged period of time. Two or more pellets (50 mg or more) may continue to release the hormone for 76 weeks or longer. Common clinical practice of pellet insertion every 6 months may therefore result in a cumulative dose, high plasma estrogen concentrations and hyperstimulation of the endometrium in women with intact uterus.

Estradiol from the pellet is absorbed directly into systemic circulation, similarly to physiologic ovarian secretions, bypassing gastrointestinal system and the first passage through the liver, and consequently, undergoing less conjugation and less conversion

to estrone. As a result, plasma estradiol, is predominantly elevated and estradiol : estrone ratio is physiologic.

As a method of long-term hormone replacement therapy pellets seem to offer several theoretical and practical advantages over a standard oral route of administration. It remains to be proven, however, whether the use of parenteral "natural" estrogens is associated with a lower incidence of adverse effects than the administration of synthetic oral preparations. The effect of estradiol pellets is longlasting, making them a simple and economical method of treatment and the plasma estradiol concentrations observed after insertion of one to three pellets remain within the physiologic range. However, continuous uninterrupted elevation of plasma estradiol over a period of more than a year cannot be considered entirely physiologic and even though it should be counteracted by a cyclic progestogen administration, it may be of a potential hazard.

Testosterone pellets do not appear to add much benefit to estrogen replacement and on the contrary, by elevating plasma estrone levels, may alter physiologic $E_2 : E_1$ ratio achieved with estradiol pellets.

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