Long-Term Hormone Implant Therapy—Hormonal and Clinical Effects

D. H. BARLOW, BSc, MD, H. I. ABDALLA, MBChB, A. D. G. ROBERTS, MBChB, F. AL AZZAWI, MBChB, I. LEGGATE, BSc, PhD, AND D. M. HART, MD

Long-term effects of hormone implants (estradiol or estradiol plus testosterone) were examined in 75 menopausal women. Both therapies relieved vasomotor symptoms with a return of significant flushing after six months, thus reimplantation was performed every six months. Estradiol levels had not returned to baseline by six months, and significant accumulation of estradiol occurred by three years. The patients given testosterone experienced a similar accumulation of testosterone. There was no significant change in mean weight, blood pressure, or liver function tests during three years. Both therapies reversed the bone biochemical changes of menopause, and in both groups there was no significant loss in bone density. Supplementation of estradiol with testosterone in implant therapy was not observed to provide additional benefit in terms of the parameters studied. *(Obstet Gynecol 67:321, 1986)*

Steroid implant therapy is popular with menopause clinic patients and provides reliable relief from a wide spectrum of climacteric symptoms.[1] In recent years it has been shown to better reproduce the premenopausal balance of estradiol and estrone[2] than oral therapies.[3] The addition of testosterone to estradiol for implantation is based on the reputed libido-improving effect of testosterone.[4,5]

Implantation is particularly suitable for hysterectomized patients, as nonhysterectomized women must receive intermittent courses of oral progesterone to prevent endometrial hyperplasia.[6] When 50-mg estradiol implants are used to provide long-term replacement, the request for reimplantation tends to be at six months because of a return of symptoms at five to seven-month intervals.[1] The hormone levels achieved with a single estradiol implant have been documented,[2] but the long-term effects of repeated implantation have not been studied in depth. The aim of the present work is to examine the effects of administration of estradiol implants every six months or combined estradiol plus testosterone implants during three years.

From the Menopause Clinics, and Department of Clinical Biochemistry, Stobhill General Hospital and Western Infirmary, Glasgow, Scotland.

Materials and Methods

Ninety-six patients were recruited from the menopause research clinics at the Western Infirmary and Stobhill General Hospital, Glasgow, and were randomly allocated to receive either 50-mg estradiol implants (estradiol group) or 50-mg estradiol plus 100-mg testosterone implants (estradiol-testosterone group) repeated at six-month intervals in response to symptoms. The three-year prospective study was completed by 75 women (estradiol group = 36, estradiol-testosterone group = 39), and the reasons for patients not completing the three-year study are listed in Table 1.

The two groups studied were similar (Table 2), and all exhibited menopausal elevation of gonadotropins at the start of the study. The estradiol and estradiol-testosterone groups lost three and one intact uterus cases by dropout, respectively. The women with an intact uterus received a seven-day course of norethisterone 5 mg daily at two-month intervals, which were timed to ensure that the patient would be off the progestogen for at least one month at each clinic visit.

Each patient attended for baseline assessment and then at two, six, eight, 12, 18, 24, 30, and 36 months after the first implant. At each visit a fasting venous blood sample was obtained, and sera and plasmas were stored at −20°C. At each visit flush symptomatology was assessed, the patient was weighed, and blood pressure was measured seated. Bone mineral content was assessed by single-beam photon absorptiometry, and measured at the midpoint of the third metacarpal by the method of Shimmins et al.[7]

The estradiol and testosterone estimations were by

0029-7844/86/$3.50

Table 1. Reason for Discontinuing Implantation

Reason	E group	ET group
Intolerance of side effects		
Breast symptoms	1	3
Uterine bleeding	3	1
Concomitant conditions or symptoms		
Chest pain	1	1
Psoriasis	1	
Leg pain	1	
Rectal bleeding		1
Recurrent backache	1	
Had pelvic floor repair and discontinued therapy	1	
Nonmedical reasons	3	3
Total	12	9

E = estradiol; ET = estradiol-testosterone.

radioimmunoassay methods as described.[8] A Standard Technicon AutoAnalyser was used to estimate calcium, inorganic phosphate, alkaline phosphatase, creatinine, albumin, and liver function tests. Serum calcium was corrected for the albumin concentration. Urinary hydroxyproline concentrations were measured by the method of Stegemann and Stalder.[10] The ratios of calcium to creatinine and hydroxyproline to creatinine were calculated. The clearance ratio of phosphate to creatinine also was calculated and the renal tubular reabsorption of phosphate ($TmPO_4/GFR$) thus derived.[11]

The effect of an individual treatment with time was tested using Student *t* test for paired data, with the patient's pretreatment level serving as a control value. Comparison between forms of therapy was by Student *t* test for unpaired data and by analysis of variance.

Results

Flush symptoms were recorded on a three-point scale according to each patient's subjective assessment of

Table 2. Parameters of Patient Groups*

Parameter	E group	ET group
N	36 (12)	39 (9)
Intact uterus	0 (3)	4 (1)
Hysterectomy only	4 (1)	4 (1)
Hysterectomy and oophorectomy	32 (8)	31 (7)
Mean age at menopause	42.9 ± 4.8	42.0 ± 6.2
Age range (yr)	31–50	33–49
Mean age at start of study	43.9 ± 4.8	45.2 ± 6.8
Mean menopause to treatment interval	1.6 ± 2.4	3.1 ± 4.3
Mean height (m)	160.3 ± 4.9	160.6 ± 5.5
Mean weight (kg)	63.1 ± 10.7	64.4 ± 8.0

See Table 1 for abbreviations.
* Dropout numbers in parentheses.

Table 3. Flush Scores in Patients Receiving Six-Month Estradiol or Estradiol-Testosterone Implants*

Months	Flush score (mean ± SEM) E (*N* = 36)	Flush score (mean ± SEM) ET (*N* = 39)
0	2.50 ± 0.27	2.13 ± 0.23
2	0.25 ± 0.09	0.30 ± 0.11
6	0.86 ± 0.12	0.80 ± 0.16
8	0.46 ± 0.12	0.36 ± 0.10
12	0.91 ± 0.13	0.82 ± 0.17
24	0.76 ± 0.13	0.81 ± 0.18
36	0.96 ± 0.17	1.00 ± 0.25

See Table 1 for abbreviations.
* Scoring based on severity rating; maximum severity = 3.

severity (Table 3). In both groups, the mean flush score was high before treatment and was near zero by two months on treatment. By six months, when reimplantation was being requested, there had been a significant increase in the flush score ($P < .05$ for both groups). A similar pattern of flushing was seen with the second implant with a significant rise in the flush score at 12 months compared with eight months ($P < .05$ for both groups). The flush scores at 24 and 36 months were similar to those at six and 12 months.

Plasma estradiol was significantly elevated ($P < .001$) above the pretreatment baseline at all intervals measured up to three years (Table 4). In both groups mean estradiol at 36 months (six months after the sixth implant) was significantly higher ($P < .001$) than at six months, indicating an accumulation of estradiol with repeated implants. There was no overall difference in the estradiol profile, comparing the estradiol and estradiol-testosterone treatment groups. The range of estradiol levels on treatment was wide and similar in both groups so that by 36 months on treatment the ranges of plasma estradiol were 322 to 1158 pmol/L (estradiol group) and 228 to 1227 pmol/L (estradiol-testosterone group).

The plasma testosterone profile (Table 5) remained unchanged over the three years in the estradiol group. In the patients receiving testosterone implants (the estradiol-testosterone group) there was evidence of accumulation of testosterone. At six months mean testosterone was significantly elevated ($P < .01$) above the pretreatment baseline, and the second implant produced a further testosterone rise. In the longer term, mean T levels at 24 and 36 months were both significantly higher ($P < .005$) than at 12 months. The mean estradiol and testosterone levels were not different when the dropout cases were included.

The marked rise in steroid hormone levels did not significantly affect body weight over the three years. The pretreatment mean weights were 63.1 ± 10.7 kg

Table 4. Plasma Estradiol Levels in Patients Completing the Three-Year Study*

Months	E implant group (pmol/L) $N = 36$	ET implant group (pmol/L) $N = 39$
0	175 ± 67	176 ± 49
2	491 ± 214	477 ± 257
6	404 ± 132	412 ± 139
8	536 ± 136	711 ± 283
12	505 ± 158	562 ± 277
24	590 ± 206	585 ± 165
36	669 ± 211	614 ± 222

See Table 1 for abbreviations.
* Mean ± SD.

(SD) (estradiol group) and 62.7 ± 11.5 kg (estradiol-testosterone group), and at three years the weights were 65.2 ± 11.0 kg (estradiol group) and 64.4 ± 11.3 kg (estradiol-testosterone group). Four women in each group had a 10% weight gain, and three and two women in the estradiol and estradiol-testosterone groups respectively had a 10% weight loss.

There was no significant effect on blood pressure on either therapy. Over three years there was a similar tendency for pressures to fall or rise in both groups. There was a significant negative correlation between initial diastolic pressure and the change in pressure over three years (estradiol group $R = -0.57$, $P < .001$; estradiol-testosterone group $R = -0.60$, $P < .001$), indicating a tendency for the pressures to revert toward the mean.

There was no significant elevation of γ-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, or bilirubin in either treatment group over the three years except in two women (one from each group). Both admitted to excessive alcohol consumption and were excluded from the liver function test analysis.

Within two months of starting therapy there were significant reductions in circulating calcium and phosphate in both groups (Table 6). Urinary calcium creatinine ratio was significantly reduced only in the estradiol group, but $TmPO_4/GFR$ was reduced in both. The estradiol and estradiol-testosterone groups showed a similar progressive fall in serum alkaline phosphatase and the hydroxyproline creatinine ratio fell significantly by six months and remained thus over two years of observation.

The pretreatment bone densities of the groups were not significantly different. Over three years in the estradiol group there was no significant change in density (−0.8%), and in the estradiol-testosterone group the mean percentage change was +2.5%, which was a significant rise ($P < .05$). There was no significant difference in the mean percentage change comparing the two treatment groups (Table 7).

Discussion

The data presented indicate that implantation with testosterone in women receiving estradiol implants did not affect circulating estradiol levels but did produce an accumulation of plasma testosterone during three years. Although no patient noted an excess of hair growth, these women were exposed to chronically elevated androgen levels. Although the value of estradiol-testosterone implants in treating loss of libido has been demonstrated,[1,4,5] a detailed assessment of the effect of implant therapy on sexual dysfunction in postmenopausal women indicated that estradiol implantation was beneficial and that estradiol-testosterone did not achieve better results.[12] The authors suggest that where implants are to be used, the first option should be estradiol alone. Testosterone should be tried only as a supplement when sexual dysfunction has not responded to therapy with estradiol implantation, because current evidence does not exclude the possibility that some individuals may benefit from the testosterone supplementation.

The authors prefer to restrict the implant therapy principally to hysterectomized women, thus avoiding problems of patient noncompliance in taking progestagen supplements. Some groups do not apply this restriction and report difficulties with progesterone side effects.[13] In the present study, for example, four of the eight nonhysterectomized women left the study because of dislike of uterine bleeding. If a patient on oral therapy dislikes uterine bleeding or other progestagen side effects, the therapy can be discontinued when she declines treatment, but the implant patient who declines further progestagen faces many months of estrogen stimulation of the endometrium. Because implant therapy provides relief from a wide

Table 5. Plasma Testosterone Levels in Implant Patients Completing the Three-Year Study*

Months	E Implant group (nmol/L) $N = 36$	ET Implant group (nmol/L) $N = 39$
0	1.62 ± 0.43	1.49 ± 0.42
2	1.79 ± 0.59	3.70 ± 1.00
6	1.75 ± 0.39	1.96 ± 0.69
8	1.69 ± 0.54	4.79 ± 2.27
12	1.70 ± 0.52	1.96 ± 0.77
24	1.36 ± 0.35	2.89 ± 0.79
36	1.61 ± 0.58	2.56 ± 1.09

See Table 1 for abbreviations.
* Mean ± SD.

Table 6. Effect of Implants of Estradiol or Estradiol-Testosterone on Biochemical Parameters of Bone Metabolism*

Biochemical parameters	Implant type	Months 0	2	6	36
Serum					
Calcium	E	2.42 ± 0.01	2.37 ± 0.01†	2.36 ± 0.01†	2.34 ± 0.02†
mmol/L	ET	2.43 ± 0.02	2.35 ± 0.02†	2.36 ± 0.01†	2.35 ± 0.02†
Phosphate	E	1.18 ± 0.03	1.03 ± 0.03†	1.05 ± 0.03†	1.00 ± 0.03†
mmol/L	ET	1.18 ± 0.03	1.00 ± 0.03‡	1.06 ± 0.03	0.94 ± 0.03†
Alkaline phosphatase	E	77.5 ± 3.9	75.9 ± 4.2	67.9 ± 4.0†	58.4 ± 2.8†
IU/L	ET	87.2 ± 7.8	73.9 ± 6.2	69.2 ± 6.4	54.8 ± 3.5†
Urinary					
Calcium creatinine ratio	E	0.405 ± 0.053	0.270 ± 0.034†	0.282 ± 0.042‡	0.264 ± 0.024†
mmol/mmol	ET	0.262 ± 0.035	0.200 ± 0.022	0.233 ± 0.028	0.282 ± 0.045
Tubular maximum for phosphate reabsorption	E	1.127 ± 0.055	0.945 ± 0.045†	1.070 ± 0.071	0.934 ± 0.038†
	ET	1.214 ± 0.067	0.971 ± 0.052	0.962 ± 0.037‡	0.852 ± 0.032‡
					24 months
Hydroxyproline creatinine ratio	E	0.030 ± 0.003	0.020 ± 0.002†	0.019 ± 0.002†	0.019 ± 0.002†
mmol/mmol	ET	0.026 ± 0.003	0.022 ± 0.002	0.019 ± 0.002	0.017 ± 0.002

See Table 1 for abbreviations.
* Mean ± SEM.
† Change relative to pretreatment, $P < .01$.
‡ Change relative to pretreatment, $P < .01$.

spectrum of symptoms in menopausal women[1] it is worthwhile considering this form of therapy in women not tolerating oral hormone replacement, as the less fluctuant hormone levels and the estrogen balance more closely resembling the premenopausal state[2] may induce greater toleration of the therapy.[13]

The study demonstrates that implant therapy as currently practiced leads to a long-term increase in plasma estradiol levels whether or not testosterone is added. The common practice of reimplantation at the time of symptom recurrence usually leads to requests for reimplantation at approximately six-month intervals using the 50-mg estradiol implant. The cross-sectional data of Cardozo et al[13] suggested that estradiol did not accumulate over three years, but the longitudinal series presented herein with a larger number of hormone measurements at each interval does demonstrate accumulation. The implants relieve a wide spectrum of menopausal symptoms,[1] including vasomotor effects. The vasomotor symptom assessment presented confirms that the requests for reimplantation occurred when flushes were returning but were less severe than before the first implant. This raises the interesting question as to the mechanism of a return of flushing at circulating estradiol levels in the reproductive range. Thom et al[2] demonstrated that a 50-mg estradiol implant produces an elevation in plasma estradiol which plateaus for four to five months before declining. It may be that the start of the fall in plasma estradiol from a very consistent level induces vasomotor instability despite the level of estradiol not being low. It is clear that further boosting the estradiol level by reimplantation relieves the symptoms once more. Reimplantation when the previous implant still functions may be responsible for the accumulation of estradiol. It is of some reassurance that the rising estradiol baseline was not associated with any adverse change in blood pressure, weight gain, or liver function tests.

Table 7. Metacarpal Mineral Content in Implant Treatment Groups*

Time	E group $N = 36$	ET group $N = 39$
0	46.85 ± 5.18	44.09 ± 5.81
2	46.99 ± 5.71	44.56 ± 5.01
6	46.69 ± 5.72	45.10 ± 5.36
8	48.03 ± 6.03	45.11 ± 5.72
12	48.19 ± 5.83	45.49 ± 5.43
24	47.12 ± 4.95	45.41 ± 5.12
36	46.36 ± 4.96	45.36 ± 4.73
Mean percentage change over 3 yr	−0.8%	±2.5%

See Table 1 for abbreviations.
* Estradiol, 50 mg; estradiol-testosterone, 50–100 mg.

It is known that bilateral oophorectomy induces a negative calcium balance with increased serum calcium and phosphate and altered urinary calcium and phosphate clearances.[14] There is increased bone resorption[15] and evidence that sensitivity to parathyroid hormone is increased.[16] Estrogen administration can reverse these biochemical changes,[17] and in the present study this estrogenic effect was observed with both treatments with the exception of the effect on

urinary calcium excretion. Both therapies reduced serum calcium and had a hypophosphatemic, hyperphosphaturic effect. Urinary calcium excretion was reduced on estradiol therapy only, but the profiles were similar in both groups from two months. The reduction in serum alkaline phosphatase activity suggests reduced bone turnover as does the reduction in excretion of hydroxyproline, which is derived largely from breakdown of bone. The data indicate that the effects achieved are sustained long term.

The assessment of bone density, by single-beam absorptiometry of the third metacarpal provides accurate information on mineral mass at the scan site and correlates well with long bone weight and total body calcium, but the measurements correlate less well with spinal bone density.[18] Despite this recognized limitation the technique has been applied widely in studies on bone density. The authors previously have applied the technique to study bone density change after oophorectomy.[17] Significant reductions in bone density occurred with a high loss over the first three years after oophrectomy (9.3%) and a lower loss between the third and sixth years (1.6%).[17] In the present study the estradiol and estradiol-testosterone groups were 1.6 and 3.1 years after menopause respectively at the start of treatment. The estradiol group was thus within the more rapid loss phase but did not lose bone density, and the estradiol-testosterone group which was in a less rapid loss phase was thus able to demonstrate a small increase in bone density. The effect can therefore be explained on the basis of the effect of estradiol in both groups.

Thus, estradiol implants prevented the significant bone changes that occur after menopause, but additional testosterone did not significantly augment this effect.

References

1. Brincat M, Magos A, Studd JWW, et al: Subcutaneous hormone implants for the control of climacteric symptoms. Lancet 1:16, 1984
2. Thom MH, Collins WP, Studd JWW: Hormonal profiles in postmenopausal women after therapy with subcutaneous implants. Br J Obstet Gynaecol 88:426, 1981
3. Anderson ABM, Sklovsky E, Sayers L, et al: Comparison of serum oestrogen concentrations in postmenopausal women taking oestrone sulphate and oestradiol. Br Med J 1:40, 1978
4. Studd JWW, Collins WP, Chakravarti S, et al: Oestradiol and testosterone implants in the treatment of psychosexual problems in the post-menopausal woman. Br J Obstet Gynaecol 84:314, 1978
5. Schleyer-Saunders E: Social and gerontological problems of the menopause: Hormone implants, The Menopausal Syndrome. Edited by Greenblatt RB, Mahesh VB, McDonough PG. New York, Medcom Press, 1974, pp 88–94
6. Paterson MEL, Wade-Evans T, Sturdee DW, et al: Endometrial disease after treatment with oestrogens and progestogens in the climacteric. Br Med J 1:822, 1980
7. Shimmins J, Anderson JB, Smith DA, et al: The accuracy and reproducibility of bone mineral measurements "in vivo": (b) methods using sealed isotope sources. Clin Radiol 23:47, 1972
8. Grant JK, Beastall GH: Clinical Biochemistry of Steroid Hormones. Methods and Applications. London, Croom Helm, 1983, pp 252–261
9. Imrie CW, Allam BF, Ferguson JC: Hypocalcaemia of acute pancreatitis: The effect of hypoalbuminaemia. Cur Med Res Opin 4:101, 1976
10. Stegemann HG, Stalder K: Determination of hydroxyproline. Clin Chim Acta 18:267, 1967
11. Bijnvoet OLM, Morgan DB: The tubular reabsorption of phosphate in man, Phosphate et Metabolisme Phosphocalcique: Regulation Normale et Aspects Physiopathologiques. Edited by DJ Hioco. Paris, Sandoz, 1971, pp 153–180
12. Dow MGT, Hart DM, Forrest CA: Hormonal treatments of sexual unresponsiveness in postmenopausal women: A comparative study. Br J Obstet Gynaecol 90:361, 1983
13. Cardozo L, Gibb DMF, Tuck SM, et al: The effects of subcutaneous hormone implants during the climacteric. Maturitas 5:177, 1984
14. Gallacher JC, Young MM, Nordin BEC: Effects of artificial menopause on plasma and urine calcium and phosphate. Clin Endocrinol 1:57, 1972
15. Nordin BEC, Aaron J, Speed R, et al: Bone formation and reabsorption as the determinants of trabecular bone volume in postmenopausal osteoporosis. Lancet ii:277, 1981
16. Heaney RP: A unified concept of osteoporosis. Am J Med 39:877, 1965
17. Lindsay R, Hart DM, Aitken JM, et al: Long term prevention of postmenopausal osteoporosis by oestrogen. Lancet i:1038, 1976
18. Stevenson JC, Banks LM, Freemantle C, et al: Regional variations in bone density in relation to total body calcium in the early post-menopausal period. Maturitas 6:193, 1984

Address reprint requests to:
David H. Barlow, MD
Nuffield Department of Obstetrics and Gynecology
University of Oxford
Headington, Oxford OX3 9DU
England

Submitted for publication August 14, 1984.
Revised July 29, 1985.
Accepted for publication August 6, 1985.

Copyright © 1986 by The American College of Obstetricians and Gynecologists.