Clinical Endocrinology (1995) 42, 445–450

Audit in Endocrinology

An audit of oestradiol levels and implant frequency in women undergoing subcutaneous implant therapy

H. M. Buckler, P. K. Kalsi, J. A. Cantrill* and D. C. Anderson

*University Departments of Medicine and *Pharmacy, Hope Hospital, Salford, UK*

(Received 28 June 1994; returned for revision 8 August 1994; finally revised 21 December 1994; accepted 24 January 1995)

Summary

OBJECTIVES The aim of the study was to review our long-term use of subcutaneous oestradiol (E_2) implant therapy for the treatment of climacteric symptoms in post-menopausal women. On the grounds that the aim is to restore premenopausal serum E_2 levels, our declared clinical policy is not to repeat implants even in the presence of symptoms if serum E_2 levels are >400 pmol/l. Therapy was with 50 mg E_2 implants inserted subcutaneously in the lower abdominal wall.

DESIGN All women who had attended the gynaecological/endocrinological clinic who had received subcutaneous E_2 implants for the relief of climacteric symptoms between December 1981 and 1992 were included.

RESULTS Between December 1981 and December 1992, 275 women received a total of 759 50 mg E_2 implants. The median length of implant therapy was 34·2 months (range 3·7–109·5 months), and the median number of implants per patient was 4 and ranged from 1 to 13. One hundred and twenty-nine women had more than four implants and their mean recorded serum E_2 level was 425 ± 187 (mean ± SD) pmol/l; the mean level over the first 24 months of therapy was 408 ± 157 pmol/l. This was not different from the mean value of the remaining period of therapy (439 ± 168 pmol/l). Following the second implant there was no significant progressive rise in serum E_2 with time and implant number and the mean E_2 level per patient was no higher in those patients who received implants more frequently. The mean time between the first two implants was 9·7 ± 0·4 months and between subsequent ones was 11·7 ± 0·5 months. After the first two implants there was no progressive change in this interval with time.

CONCLUSION This study shows that effective, safe and sympathetic management of women with oestrogen deficient symptoms may be achieved by use of two criteria to determine re-treatment; the return of symptoms, and a serum E_2 level no higher than 400 pmol/l. Once therapy is established, E_2 implants may need to be prescribed only on an annual basis. There appears to be no justification for giving E_2 implants more frequently as this policy achieves satisfactory (physiological) premenopausal E_2 levels and good symptomatic relief without any evidence for accumulation of E_2 or 'tachyphylaxis'.

The ideal management of patients presenting with symptoms of oestradiol (E_2) deficiency would be the maintenance of plasma E_2 levels within the physiological premenopausal range with the concomitant absence of symptoms. Oestrogen can be administered orally, percutaneously, or subcutaneously in the form of implants. The latter method provides reliable symptomatic relief (Brincat *et al.*, 1984; Cardozo *et al.*, 1984; Thom *et al.*, 1981) and conserves post-menopausal bone mass (Savvas *et al.*, 1988; Garnett *et al.*, 1991). Administration of oestradiol via implants has several advantages over the other routes, including avoidance of the enterohepatic circulation, reduction of gastrointestinal symptoms, the achievement of a near physiological ratio of E_2 to oestrone, convenience, and good compliance.

In most clinics, implants are repeated at periods of 6 months or less (Brincat *et al.*, 1984; Cardozo *et al.*, 1984; Gangar *et al.*, 1989) and new implants tend to be inserted when symptoms recur. Cross-sectional studies suggest that following such a policy seems to result in a progressive rise in plasma E_2 (Savvas *et al.*, 1988; Gangar *et al.*, 1989). Longitudinal studies have shown that E_2 levels do not return to pretreatment levels 6 months following a single 50-mg E_2 implant (Thom *et al.*, 1981; Barlow *et al.*, 1986; Buckler *et al.*, 1993) and that levels were significantly higher than pretreatment levels 6 months following the final implant after 3 years of continued implant treatment (Barlow *et al.*, 1986). These studies suggested that symptoms return when the plasma E_2 concentrations start to fall, not when a post-menopausal value has been reached. Repeat implantation based on the recurrence of symptoms alone may therefore result in some patients developing supraphysiological concentrations of E_2. This has led to concern about drug dependency with hormone replacement therapy (Bewley & Bewley, 1992).

Correspondence: Dr H. M. Buckler, Department of Endocrinology, Hope Hospital, Eccles Old Road, Salford M6 8HD, UK.

It has been declared policy in our clinic that E_2 implants are not to be repeated until the level of serum E_2 has fallen below 400 pmol/l, even in the presence of symptoms, regardless of when the previous implant was given. This policy has been followed in an attempt to prevent the development of supraphysiological E_2 levels and the need for more and more frequent reimplantation in women receiving E_2 implant therapy. In order to assess the clinical use and effectiveness of E_2 implant therapy in our clinic we have performed an audit on all E_2 deficient women who had received subcutaneous E_2 implants.

Aims

(1) To audit the long-term use of subcutaneous oestradiol (E_2) implant therapy in women.
(2) To investigate how successful is this form of treatment in achieving normal (premenopausal) E_2 levels.
(3) To examine for any evidence of 'tolerance' to E_2 implants.

Methods

An audit was undertaken on all women who had attended the gynaecological/endocrinological clinic at Hope Hospital, Salford, presenting with symptoms of oestrogen deficiency, and who were subsequently treated with hormone implant therapy from December 1981 up to December 1992. Patients were identified from records of all implants undertaken and by screening patient notes over a one-year period as they attended the clinic. The audit comprised data regarding previous medical history, dates of previous implants, pre and post-implant symptoms, plasma levels of E_2 and testosterone (T), and any complications of therapy. The data were recorded on a purpose-designed data base and spreadsheet using Smart II.

Therapy was with 50 mg E_2 implants (Organon Laboratories UK) implanted subcutaneously in the lower abdominal wall. Where reduced libido or breast discomfort was a problem, a 100-mg T implant was given as well. Implants were not repeated until the E_2 level was <400 pmol/l. From 1981 to 1988 women were reviewed at 3-month intervals and plasma E_2 levels were measured at each visit. After 1988 follow-up was 6-monthly. All women receiving E_2 implant therapy were sampled. If the patient had not had a hysterectomy, an oral progestogen was added to therapy for 12 days each month ($n = 130$).

Data collected from 75 normal ovulatory cycles as determined by serial ultrasound scans was used to determine normal 'premenopausal' E_2 levels (Buckler *et al.*, 1991). Plasma E_2 was measured by RIA from samples collected on alternate days over one cycle. The data were normalized around the LH surge which was called day 0. The E_2 level was lowest on day −14 of the cycle (150 pmol/l, range 90–257) and rose to 761 pmol/l (range 305–2096). The mean E_2 level over the entire cycle was 349 pmol/l.

Radioimmunoassays

Oestradiol was measured by radioimmunoassay (Steranti E_2 direct kit, Steranti Research Ltd) up to 1989. The within assay coefficient of variation (CV) in the range 100–1500 pmol/l was <12% and between assay CV was <10% in the range 300–1500 pmol/l. Sensitivity was 37 pmol/l and there was no significant cross-reactivity with synthetic oestrogens, progesterone or testosterone. From 1989 to 1992 the Cis Soren direct E_2 method was used. Within assay CV was <10% in the range 150–2000 pmol/l and between assay CV was <12% in the range 140–1320 pmol/l. There was no significant cross-reactivity with synthetic oestrogens, progesterone, cortisol or testosterone and the sensitivity was 16·5 pmol/l.

Testosterone was measured by radioimmunoassay following extraction with dimethyl ether to minimize cross-reactivity. The within assay CV was <10% in the range 0·5–20 nmol/l and between assay CV was <12% in the range 2·3–23 nmol/l. Sensitivity was 0·4 nmol/l.

Statistical analysis

Analysis of the intervals between successive implants as a function of implant number was performed using paired *t*-tests. Analysis of variance was used to analyse the plasma

Table 1 Patient characteristics ($n = 275$)

Mean age at start (years)	46 (range 17–62)
Mean weight (kg)	64·9 (range 31–104)
Diagnosis	No. of patients
Menopausal symptoms	228
Premature ovarian failure	21
Gonadal dysgenesis including Turner's syndrome	5
Osteoporosis	17
Hypopituitarism	4
Hysterectomy	145 (54 alone, 91+ oophorectomy)
Testosterone	107 patients also received a 100-mg testosterone implant at some stage ($n = 242$)

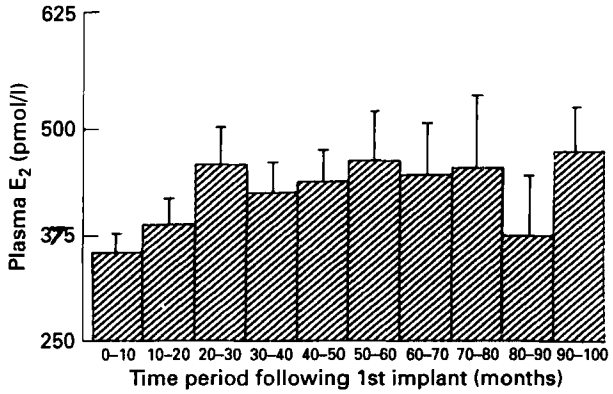

Fig. 1 Mean (± SD) serum E_2 levels plotted against time, in 10-month intervals, since receiving the first implant in all women still undergoing E_2 implant therapy, up to 100 months following first implantation. There is no progressive increase in E_2 levels with time.

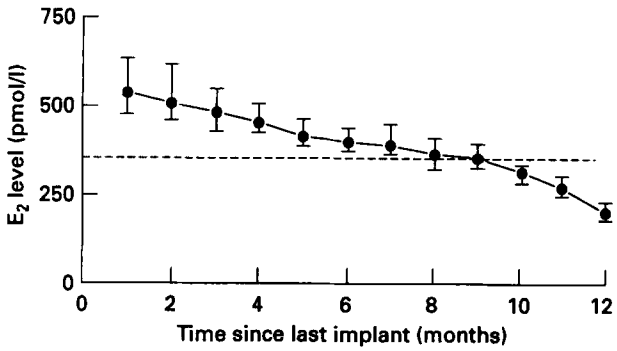

Fig. 3 Serum E_2 levels in relation to time since last implant from all patients is shown. All data are log transformed. The mean and 97% confidence limits are shown. The number of observations per time point varies from $n = 560$ (6 months) to $n = 22$ (2 months). The dotted line shows mean E_2 level per cycle from 75 normal cycles.

E_2 levels in relation to time and as a function of the intervals between implants.

Results

The first E_2 implant administered for women attending the gynaecological/endocrinology clinic at Hope Hospital was in December 1981. In the 11 years to December 1992, 275 women received a total of 759 50-mg E_2 implants. Of the total number of patients receiving implant therapy, 168 received E_2 alone and 107 received E_2 in conjunction with testosterone (100 mg) at some stage during their therapy. Patient information is summarized in Table 1.

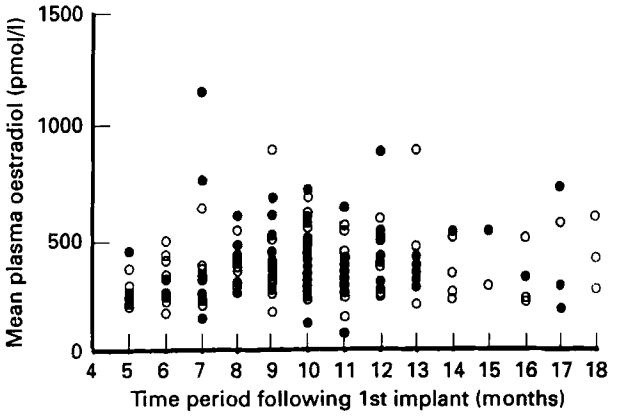

Fig. 2 Mean serum E_2 levels per patient are plotted as a function of the mean interval between implants. There is no increase in E_2 levels in those women receiving implants more frequently. Patients receiving ●, E_2 and testosterone implants; ○, E_2 alone.

The median length of implant therapy was 34·2 months (range 3·7–109·5 months) and the median number of implants per patient 4 (range 1–13).

E_2 levels

One hundred and twenty-nine women had more than 4 implants and their mean recorded serum E_2 level was 425 ± 187 pmol/l (range 190–1151). The mean serum E_2 level over the first 24 months of therapy was 408 ± 156 pmol/l (mean ± SD) and this was not significantly different from the mean value over the remaining period of therapy (439 ± 168 pmol/l). Figure 1 shows the mean serum E_2 levels in successive periods following the start of implant therapy in all patients. Following the second implant there was no significant progressive rise in serum E_2 with time and implant number. The mean E_2 level per patient was no higher in those patients who received

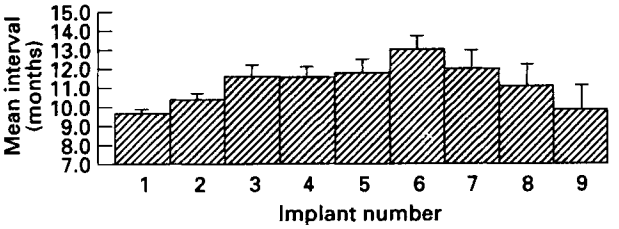

Fig. 4 The mean interval (months) between re-implantation is shown as a function of the number of implants received. There is a significant increase in the implant interval between first and second implants and subsequent ones. After the first two implants there is no change in the interval between implantation (mean ± SD is shown).

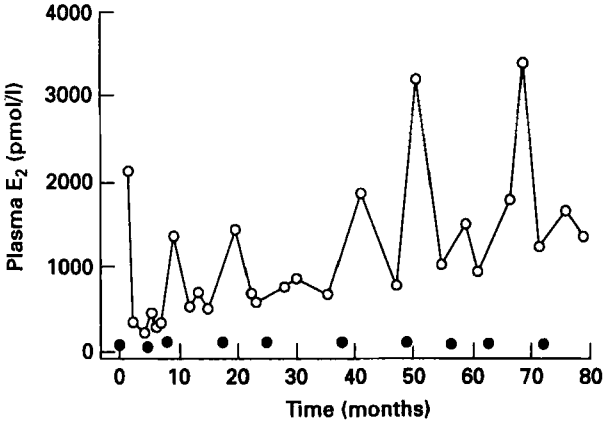

Fig. 5 Serum E_2 levels in a patient who appears to have become an 'oestradiol addict'. ●, The times that 100-mg E_2 implants were re-implanted. There is a progressive rise in serum E_2 levels with time.

implants more frequently (Fig. 2). In Fig. 3 are shown the mean E_2 levels in relation to time of last implant for all patients. It shows that the E_2 level rose to a peak at one month post implant and gradually declined over the next 12 months. A hypothetical level of 349 pmol/l has been calculated for comparison, as a mean premenopausal level, as described earlier. Oestradiol levels do not fall to below this until 10 months post implantation.

Implant frequency

The mean frequency of E_2 implantation in all patients was $10{\cdot}9 \pm 2{\cdot}8$ months (mean ± SD). The frequency of implantation was no different in those women receiving E_2 alone ($11{\cdot}9 \pm 3{\cdot}0$ months) than in those receiving both (E_2 and T) implants ($10{\cdot}8 \pm 2{\cdot}5$ months).

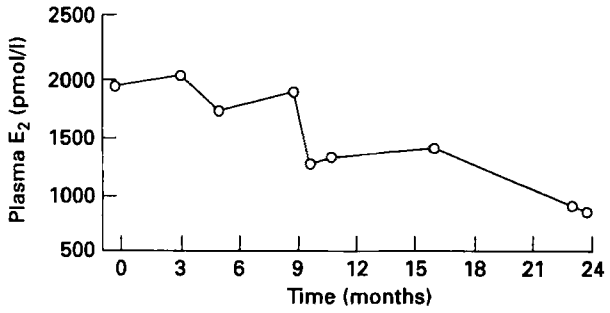

Fig. 6 An example of the problem of frequent implants given purely according to patient's symptoms. She had 50-mg E_2 implants about every 3 months for 2 years before we first saw her at time 0. E_2 levels declined slowly from 2000 to 900 pmol/l over 2 years, despite no further implants.

Analysis of the intervals between successive E_2 implants is shown in Fig. 4. The interval between the first and second implants was $9{\cdot}7 \pm 3{\cdot}4$ months and although the interval significantly increased between the first and third implant ($P < 0{\cdot}01$) there was no subsequent change with time in the intervals between implants. The mean interval between implants after the third implant was $11{\cdot}7 \pm 2{\cdot}5$ months.

Testosterone implantation

One hundred and seven of the patients on E_2 implants also received a total of 242 testosterone implants. The mean post-implant plasma T levels in these patients was $3{\cdot}5 \pm 0{\cdot}2$ nmol/l (298 total measurements).

Individual cases

Although the mean E_2 levels seen in this study were in the 'premenopausal' range the occasional supraphysiological level was seen. Two cases are described which proved a particular problem.

Case A. The first case is a 49-year-old woman who was referred with a long history of 'gynaecological' problems for which she had separately had a vaginal hysterectomy and then bilateral oophorectomy. She gave a long history of dissatisfaction with her hormone replacement therapy and before referral had received an E_2 implant to keep her HRT under control. She is now receiving E_2 implants (100 mg) every 6 months and an unknown amount of oral oestrogens (Premarin, Wyeth Laboratories UK) prescribed, reluctantly, by her general practitioner. Her hormone profile is shown in Fig. 5. This shows extremely high E_2 levels with an overall progressive rise in her E_2 levels.

Case B. This 55-year-old woman was referred to us when she moved into the area in 1989. Since 1982, at another centre, she had been receiving 50-mg E_2 implants when her symptoms returned, about every 3–6 months. When first seen by us, the serum E_2 level was 2030 pmol/l (Fig. 6). Her E_2 level remained well above physiological levels for over 2 years without any further E_2 therapy. An implant was not repeated until the E_2 levels fell below 400 pmol/l and, despite this, she felt better and was free of symptoms.

Symptoms

Most patients received good symptomatic relief of their menopausal symptoms and opted to continue with E_2 implant therapy until HRT was stopped.

Hot flushes was the commonest symptom complained of prior to treatment (Table 2). Oestradiol implant therapy produced good relief of this symptom. Table 2 shows the

Table 2 Symptoms prior to first implant and after 50 months therapy ($n = 103$)

Symptom*	Prior to first implant (%)	At 50 months implant therapy (%)
Hot flushes	89	15
Depression	29	–
Lassitude/lethargy	24	3
Vaginal dryness	23	–
Low libido	21	2
Palpitations	12	–
Irritability	10	5
Anxiety	10	3
Dyspareunia	10	–
Emotional lability	6	–
Breast discomfort	6	5
Pain (abdominal, back)	5	2
Headaches	5	4
Bloating	3	–
Nausea	3	–

*The 13 commonest symptoms complained of prior to treatment are listed. The percentage of women complaining of these prior to treatment and then after 50 months E_2 implant therapy are shown. Only those women who continued to receive treatment for 50 months are included.

symptom profile of 103 women undergoing long-term E_2 implant treatment prior to and after 50 months implant therapy. Thirty-five women received one E_2 implant only and declined further implant treatment. Their reasons for this are shown in Table 3. Return of menopausal symptoms in women with plasma E_2 levels >400 pmol/l did not appear to be a problem. Four patients discontinued concomitant testosterone implant therapy because of hirsutism but it was otherwise well tolerated.

Discussion

The Data Sheet Compendium and British National Formulary entry on E_2 implants recommends repeat implantation when symptoms return, usually at intervals of 4–8 months. This information is not only inconsistent but does not provide clear guidelines as to when implantation should occur. In clinical practice, implants in many units are administered at intervals of 6 months or less (Brincat *et al.*, 1984; Cardozo *et al.*, 1984; Gangar *et al.*, 1989).

Table 3 Reasons for discontinuing treatment in those women who received only one implant ($n = 35$)

Reason	No.
Felt better without HRT	8
Preferred other form of HRT	16
Lost to follow-up	6
No apparent benefit	3
Advised to discontinue HRT on medical advice	2

There have been reports that continuous long-term therapy with subcutaneous E_2 implants can result in supraphysiological levels of E_2 (Garnett *et al.*, 1990; Gangar *et al.*, 1989). The term 'tachyphylaxis' has been used to describe the syndrome of women requesting re-implantation within 2–3 months because of the return of symptoms. If re-implantation is performed after such a short interval there will be an increase in plasma E_2 levels. Implants repeated even at 6-monthly intervals tend to be cumulative, resulting in increasing levels of plasma E_2 (Cardozo *et al.*, 1984). Gangar *et al.* (1989) reported 12 patients with supraphysiological E_2 levels from their clinic when re-implantation has been based on the recurrence of symptoms. Garnett *et al.* (1990) found a 3% incidence of E_2 levels in excess of 1750 pmol/l in 1388 women seen during 1988. Fifty-two per cent of these women had a psychiatric history which the authors thought might be an important component.

The management of patients at Hope Hospital, Salford, with symptoms of E_2 deficiency involved re-implantation based on two criteria: the recurrence of symptoms and/or a plasma E_2 level below 400 pmol/l. The present study indicates that using these criteria, effective management of post-menopausal HRT with implants could be achieved without the need for regular implantation at 6-monthly intervals. Overall, women experienced good symptomatic relief. It may be that achievement of a more stable 'steady state' of plasma E_2 levels around the normal premenopausal range results in the development of less severe menopausal symptoms arising from rapid changes in plasma E_2 levels.

The data showed that the first two implants needed to be administered at intervals of 9 months ($9{\cdot}2 \pm 3{\cdot}4$ months) but successive implants were required only annually ($11{\cdot}7 \pm 2{\cdot}5$ months). Analysis of the post-implant E_2 levels indicates that there was no progressive increase in plasma E_2 levels with long-term treatment. Supraphysiological E_2 levels were rarely seen (2 cases).

The exceptions in whom supraphysiological levels were seen have important lessons (Cases A and B). It appears that a minority of women feel better with supraphysiological levels of E_2. Case A has proved a particular problem. After many years of trying to keep her HRT under control, she has E_2 implants of 100 mg every 6 months and an unknown amount of oral Premarin (Wyeth Laboratories UK). The

need in such cases to capitulate and opt for a policy of containment should not detract from the general principle which, if applied early, might have prevented the patient becoming an apparent 'E_2 addict'.

Case B illustrates the problems of a policy operated in many clinics—to re-implant on symptoms alone. She has settled well on our present policy and found objective knowledge of the level of the plasma E_2 in relation to physiological levels reassuring in deciding with us when implants should be repeated.

In conclusion, effective and sympathetic management of women with oestrogen deficient symptoms may be achieved by the use of two criteria together to determine re-treatment:

(a) The return of symptoms associated with

(b) A plasma oestradiol level no higher than 400 pmol/l.

Once therapy is established, oestradiol implants may need to be given only on an annual basis. This achieved satisfactory physiological ('premenopausal') plasma oestradiol levels. The policy of implanting, purely based on perceived return of symptoms without regard to the plasma oestradiol level, is illogical and may lead to accumulation and supra-physiological oestradiol levels.

Acknowledgements

We are grateful to Organon Laboratories (UK) for financial support.

References

Barlow, D.H., Abdalla, H.I., Roberts, A.D.G., Al, Azzawi, F., Leggate, I. & Hart, D.M. (1986) Long term hormone replacement therapy—hormonal and clinical effects. *Obstetrics and Gynaecology*, **67,** 321–325.

Bewley, S. & Bewley, T.H. (1992) Drug dependence with oestrogen replacement therapy. *Lancet*, **339,** 290–291.

Brincat, M., Magos, A.L., Studd, J.W.W., Cardozo, L.D., Wardle, P.D. & Cooper, D. (1984) Subcutaneous hormone implants for the control of climacteric symptoms. *Lancet*, **i,** 16–18.

Buckler, H.M., Evans, C.A., Mamtora, H., Burger, H.G.F. & Anderson, D.C. (1991) Gonadotrophin, steroid and inhibin levels with incipient ovarian failure during anovulatory and ovulatory rebound cycles. *Journal of Clinical Endocrinology and Metabolism*, **72,** 116–124.

Buckler, H.M., Rothwell, C., Hollis, S. & Robertson, W.R. (1993) Physiological oestradiol administration does not change the biological to immunological ratio of LH in serum from postmenopausal women. *Clinical Endocrinology*, **38,** 481–484.

Cardozo, L., Gibb, D.M.F., Studd, J.W.W., Tuck, S.M., Thom, M.H. & Cooper, D.J. (1984) The use of hormone implants for climacteric symptoms. *American Journal of Obstetrics and Gynaecology*, **148,** 336–337.

Gangar, K., Cust, M. & Whitehead, M.I. (1989) Symptoms of oestrogen deficiency associated with supraphysiological plasma oestradiol concentrations in women with oestradiol implants. *British Medical Journal*, **299,** 601–602.

Garnett, T., Studd, J., Watson, N. & Savvas, M. (1991) A cross-sectional study of the effects of long term percutaneous hormone replacement therapy on bone density. *Obstetrics and Gynaecology*, **78,** 1003–1007.

Garnett, T., Studd, J.W.W., Henderson, A., Watson, N., Savvas, M. & Leather, A. (1990) Hormone implants and tachyphylaxis. *British Journal of Obstetrics and Gynaecology*, **97,** 917–921.

Savvas, M., Studd, J.W.W., Fogelman, I., Dooley, M., Montgomery, J. & Murby, B. (1988) Skeletal effects of oral oestrogen compared to subcutaneous oestrogen and testosterone in post menopausal women. *British Medical Journal*, **197,** 331–333.

Thom, M.H., Collins, W.P. & Studd, J.W.W. (1981) Hormonal profiles in post menopausal women after therapy with subcutaneous implants. *British Journal of Obstetrics and Gynaecology*, **88,** 426–433.