

A comparison of 25 mg and 50 mg oestradiol implants in the control of climacteric symptoms following hysterectomy and bilateral salpingo-oophorectomy

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Objectives 1. To compare the effects of 25 mg and 50 mg oestradiol implants on serum follicle stimulating hormone and oestradiol levels; and 2. to assess the relationship of the dose of oestradiol implant and serum oestradiol on the effectiveness and duration of climacteric symptom control.

Design Randomised, double-blind investigation.

Participants Forty-four women, who had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Methods The women were randomised to receive either 25 mg ($n = 20$) or 50 mg ($n = 24$) oestradiol implants. Follow up consisted of prospective symptom enquiry and hormone assays.

Main outcome measures Primary: climacteric symptom control: duration and effectiveness; secondary: serum oestradiol and follicle stimulating hormone levels

Results Serum oestradiol was significantly higher and serum follicle stimulating hormone significantly lower after the fourth month of treatment in women receiving 50 mg implants. No significant difference in symptom control was noted in the two groups. The mean duration of symptom control was similar in the two groups: 5.9 months (SD 2.4) in those receiving 50 mg oestradiol and 5.6 months (SD 2.3) in those receiving 25 mg.

Conclusion The higher level, 50 mg oestradiol implants does not result in better control of symptoms nor in longer periods of symptom control compared with 25 mg oestradiol implants. In order to maximise compliance, 25 mg oestradiol implants should therefore be the treatment of choice for women with normal bone density seeking relief of climacteric symptoms.

INTRODUCTION

There is much evidence that hormone replacement therapy is important in the treatment and prevention of the immediate and long term complications of the menopause¹⁻³. Subcutaneous hormonal implants have been used for the relief of menopausal symptoms for many years. Greenblatt *et al.*⁴ first reported on the use of oestradiol and testosterone implants for the alleviation of climacteric symptoms. Numerous studies since then have confirmed the value of hormone implants in the treatment of climacteric symptoms and the prevention of postmenopausal osteoporosis. Some workers have used 50 mg oestradiol implants, others the 100 mg dosage, and others have used combinations of oestradiol and testosterone⁵⁻⁸.

Despite the undoubted benefits of hormone replacement therapy in general, and of oestrogen implants in particular, compliance with treatment could be better. Side effects, such as bleeding problems and mastalgia, are some of the main reasons for this poor compliance^{9,10}, leading to low uptake and high discontinuation rates¹¹. These side effects are more common in women using higher dose oestrogen therapy because of greater endometrial stimulation and direct effects on tissues such as the breast. There is also a theoretical possibility that the risks of breast cancer and venous thromboembolism with hormone replacement therapy usage may be dose-related, although data regarding this are not available. Use of the lowest effective dosage of hormone replacement therapy should therefore be encouraged until more data are available.

In view of the above, researchers have studied the effect of lower dose, 25 mg oestradiol implants, to determine whether the benefits on menopausal symptoms

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and osteoporosis are retained with the lower dosage, while side effects are minimised. This would have the benefit of improving compliance with hormone replacement therapy, prolonging its usage and maximising cost-effectiveness of therapy¹². Owen *et al.*¹³ reported the findings of an uncontrolled observational study, which suggested that 25 mg oestradiol implants might provide adequate symptom relief of the climacteric syndrome. Holland *et al.*¹⁴ confirmed that 25 mg oestradiol implants were well tolerated by older postmenopausal women, a group who are particularly sensitive to oestrogenic side effects such as mastalgia. They showed that postmenopausal osteoporosis could not only be prevented, but treatment resulted in a modest increase in bone density.

We undertook this double-blind, randomised, controlled trial to compare the effect of 25 mg oestradiol implants with the more commonly used 50 mg dosage, in the control of climacteric symptoms in women who have undergone hysterectomy and bilateral salpingo-oophorectomy. The aim of the study was to show that control of climacteric symptoms could be achieved with lower dosage implants. Adverse effects should be minimised and compliance maximised, particularly in older postmenopausal women who poorly tolerate even minimal side effects.

METHODS

A total of 44 healthy women, aged less than 65 years, who had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy for benign causes, were recruited from St. Thomas' Hospital and the menopause clinic at Lewisham Hospital. Excluded were those patients who had ever used an oestradiol implant, who had used any form of hormone replacement therapy in the previous three months, those for whom oestradiol was contraindicated or for whom concomitant testosterone was deemed necessary. Patients were randomised to receive either 25 mg or 50 mg fused crystalline oestradiol implants into the anterior abdominal wall. The implant was carried out as the patient developed climacteric symptoms, usually within one week of surgery. Ethical approval had been obtained from the local ethics committee and informed consent was obtained from all patients prior to recruitment. Both patients and study co-ordinator were blinded as to which strength implant was being administered. The doctor was assigned a computer generated randomisation code with which to allocate patients into the separate arms of the study, at the time of implant therapy.

Blood was taken for serum follicle stimulating hormone and oestradiol concentration (both free and total) before treatment and following treatment on days 1, 2, 3

and 4, weeks 1, 2, 3, 4 and 6, and monthly thereafter. Serum analysis was carried out under the responsibility of the pathology department of St Thomas' Hospital, London.

Symptoms were assessed from symptom rating scale questionnaires which were filled in prospectively by the patients before randomisation and at 14 day intervals after treatment. Although not formally validated, these questionnaires were based on the validated retrospective Kupperman index symptom rating. It was felt that a prospective patient-based symptom rating would be superior to the retrospective doctor-based rating of the Kupperman index. The hormone implantation was carried out by a doctor who was not involved in the assessment of symptom scores. The questionnaires were collected at the clinic visits at three and six months. The most severe symptoms were graded zero, and complete suppression of symptoms was graded three. Patients were asked to give scores for the following symptoms: tiredness, tension, depression, headaches, panic attacks, hot flushes, sleeping badly, joint/bone aches, loss of sexual arousal and urinary problems. Data were entered by two data analysts (twice independently from each other) in a computer database and were analysed in consultation with a medical statistician. All adverse events were recorded into the case report file by the investigator at every assessment period in the trial.

Power calculations

It was assumed that an implantation period of greater frequency than four-monthly would be regarded as being unacceptable. As the standard recommended reimplantation period for 50 mg implants is six-monthly, it was taken that a greater than two-month difference in duration of symptom control between the two preparations would be clinically significant. Using Altman's nomogram, power calculations revealed that a minimum sample size of 40 patients, 20 in each group, would have a power of 80% of detecting this difference at the 5% level of significance ($P = 0.05$). Recruitment was based on completion of 20 per group, allowing for 10% drop out.

Statistics

The serum oestradiol and follicle stimulating hormone levels and symptom rating data were not normally distributed; data for the two groups were therefore compared using the Mann-Whitney *U* test. As this was a study in which repeated measures were made on the same patients in the two groups, data analysis was also carried out using a Bonferroni correction to allow for multiple testing and also by performing repeated

measures analysis of variance. This further statistical testing revealed no significant difference in the outcome of the analysis.

RESULTS

At the end of recruitment, 21 women had been randomised into the 50 mg group and 24 into the 25 mg group. One woman in the 50 mg group was found not to have had a bilateral salpingo-oophorectomy and was therefore excluded from the analysis. There was no significant difference in age, height or weight between the two groups of women (Table 1). No significant changes were noted in blood pressure or body mass index. Marked variation was noted in the serum oestradiol and follicle stimulating hormone in the two groups. Serum oestradiol levels began to decline from the fourth month onwards in both groups. The circulating oestradiol levels remained significantly higher during the last two months of the trial in those women who received 50 mg implants, compared with those who received 25 mg oestradiol (Fig. 1). The concentration of serum follicle stimulating hormone was reduced after hormone implantation, but remained significantly higher in those women who received 25 mg implants (Fig. 2).

Control of symptoms was excellent with both doses. Good symptom control was noted within two to four weeks of treatment in both groups. There did not appear to be any significant difference in the effectiveness of control of climacteric symptoms, such as hot flushes, depression and tiredness (Table 2). The mean duration of symptom control was similar in the two groups: 5.9 months (SD 2.4) in those receiving 50 mg oestradiol and 5.6 months (SD 2.3) in those receiving 25 mg.

No serious adverse experiences were recorded. Minor adverse events were all related to the return of climacteric symptoms. These were hot flushes and sweats (one receiving 25 mg and four receiving 50 mg), mild depression (one in each group), tiredness (one receiving 25 mg) and vaginal dryness (one receiving 50 mg).

There was no statistically significant difference between the two groups in terms of frequency of adverse events or early withdrawal from treatment. The summary statistics for the total number of days in the study from implant insertion were as follows: mean 174,

Table 1. Patient's demographic data by treatment group. Values are given as median (interquartile range).

| | 50 mg (n = 20) | 25 mg (n = 24) |
|-------------|-------------------|-------------------|
| Age (years) | 46 (43-48.5) | 47 (43-51) |
| Height (cm) | 162.5 (160-168) | 163 (160-165) |
| Weight (kg) | 67.3 (63-73) | 67.5 (62-74) |

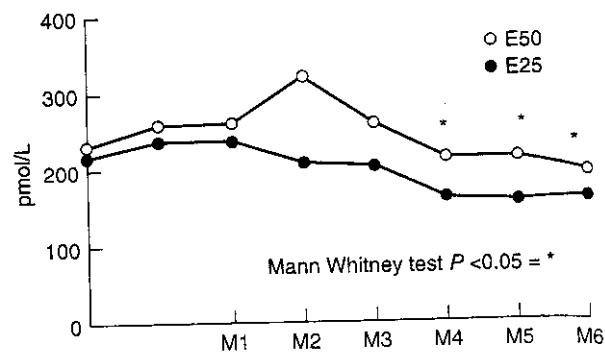


Fig. 1. Levels of oestradiol.

median 168, standard deviation 70 (range 38-317) for the 25 mg group; and mean 159, median 147, standard deviation 66 (range 63-310) for the 50 mg group. None of the women discontinued earlier than six months for reasons other than requiring further hormone replacement therapy due to return of climacteric symptoms, apart from the woman in the 50 mg group who was excluded from the analysis.

DISCUSSION

The results of this study suggest that 25 mg oestradiol implants may be as effective as 50 mg implants in controlling climacteric symptoms. Our findings correlate with those of Owen *et al.*¹³ whose findings suggested that 25 mg oestradiol implants provided adequate symptom relief of the climacteric syndrome. Our study demonstrates that the duration of symptom control also appears to be the same in both 50 mg and 25 mg dosages, despite a less significant initial suppression of follicle stimulating hormone levels and a more marked decline in the serum oestradiol levels in the fifth and sixth months after hormone implantation, recorded in women who received a dosage of 25 mg. No adverse experiences, other than return of climacteric symptoms, were observed in either treatment group.

There have been no previous studies using the crystalline form of 17 β oestradiol, but earlier work utilising the amorphous preparations has been reported. Higher dose oestradiol implants have also demonstrated the dose response effect of oestradiol implants on follicle stimulating hormone and oestradiol levels. Thom *et al.*¹⁵ reported on the hormonal profiles in women receiving subcutaneous hormone implants varying from 50 mg to 100 mg oestradiol with or without testosterone. Suppression of follicle stimulating hormone was noted within two weeks of using the 100 mg pellet and persisted for seven months. Serum oestradiol level showed considerable elevation which also persisted for seven months. With the 50 mg implant, a similar but less dra-

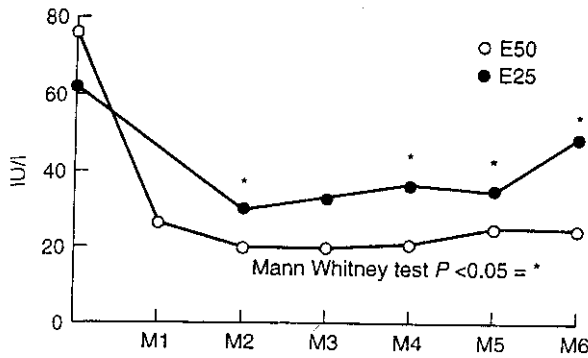
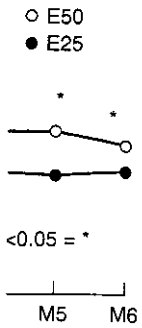


Fig. 2. Levels of follicle stimulating hormone.

matic effect on the oestradiol level was noted and the serum levels began to decrease after four months. As with our study, symptom control was of similar duration in both groups.

Our findings suggest that for most menopausal women, a relatively low serum oestradiol level is required for climacteric symptom control. The 25 mg implant dosage produces an oestradiol level which exceeds this threshold, even towards the end of the six-month treatment period. However, it was our impression that higher oestradiol levels resulted in better symptom control in some women with more resistant symptoms, suggesting some inter-individual variation in the symptom response threshold. Nonetheless, these data suggest that the 'default' dose should be 25 mg for symptom control.

Studies have shown that there is a dose-response effect of oestradiol on increasing bone density. Savvas *et al.*¹⁶ found that while oral therapy prevented further bone loss, subcutaneous hormonal implants of between 50 and 100 mg every six months will result in an increase in bone density. A prospective study by Studd *et al.*¹⁷ reported that 75 mg implants, given at six-monthly intervals, resulted in an 8.3% increase in bone density. Furthermore, it was noted that the increase in bone density correlated with the serum

oestradiol level. Notelovitz *et al.*¹⁸ compared the value of 25 mg and 50 mg implants after a surgically-induced menopause and reported that bone resorption was prevented with 25 mg implants. Holland *et al.*¹⁴ confirmed that the 25 mg oestradiol implant could prevent postmenopausal osteoporosis and result in modest increases in bone density, but that a higher dose of implant resulted in greater increase in bone density. Therefore, while 25 mg is effective in controlling climacteric symptoms and maintaining bone density, a higher dose of 50 mg or 75 mg should be recommended for women who have already sustained significant postmenopausal bone loss. This would initially increase bone density to a normal level and when the desired effect had been achieved, density could be maintained with the 25 mg dosage. However, this reduction in dose may lead to a transient return of climacteric symptoms.

Concern has been expressed that prolonged usage of hormone implants can lead to accumulation of oestradiol in the serum thus producing supraphysiological levels¹⁹. However, of 1388 women using oestradiol implants studied by Garnett *et al.*²⁰, only 3% had levels above 1750 pmol/L. Also, Savvas *et al.*¹⁶ reported that after the use of oestradiol implants for a median of eight years the median serum oestradiol level was only 725 pmol/L. Higher levels may be achieved with inappropriately frequent or high dose hormone implantation. The use of 25 mg oestradiol implants should prevent oestradiol levels from becoming supraphysiological. However, it is our experience that some women actually need higher serum levels to alleviate persistent climacteric symptoms, particularly the psychological symptoms of depression and tiredness. In these women 50 mg or even 100 mg implants may need to be given every six months. These women may also require testosterone replacement if they have persistent symptoms, such as tiredness and loss of libido, despite oestrogen implants alone. Testosterone implants should also be considered in women who have undergone a surgical menopause, as the ovaries are an important source of androgens.

Table 2. Symptom control by treatment group. Values are given as median (interquartile range).

| Symptom timing | Hot flushes | | Depression | | Tiredness | |
|----------------|-------------|-----------|------------|-------------|-----------|---------|
| | 50 mg | 25 mg | 50 mg | 25 mg | 50 mg | 25 mg |
| Week 2 | 2 (0.5-2.5) | 1.5 (1-3) | 3 (1-3) | 2 (2-3) | 1 (0.5-2) | 1 (1-2) |
| Week 4 | 3 (2-3) | 3 (2-3) | 3 (2-3) | 2 (2-3) | 2 (1-2) | 2 (1-2) |
| Month 2 | 3 (2-3) | 3 (2-3) | 3 (2-3) | 3 (2-3) | 2 (1-3) | 2 (1-3) |
| Month 3 | 3 (2-3) | 3 (2-3) | 3 (2-3) | 3 (3-3) | 2 (1-3) | 3 (2-3) |
| Month 4 | 3 (2-3) | 3 (1-3) | 3 (2-3) | 3 (2-3) | 2 (2-3) | 2 (1-3) |
| Month 5 | 3 (2-3) | 2.5 (1-3) | 3 (2-3) | 3 (2-3) | 2 (1-2) | 2 (2-3) |
| Month 6 | 2 (2-3) | 2 (1-2.5) | 2 (2-3) | 2.5 (1.5-3) | 1 (1-3) | 2 (1-3) |

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In conclusion, the higher levels of oestradiol produced by 50 mg implants do not result in better symptom control, nor in a longer period of symptom control compared with 25 mg oestradiol implants. From the results of this and other studies, we would recommend the 25 mg dosage of oestradiol implants every five to six months for those women with normal bone density for control of menopausal symptoms. This dosage should minimise any possible dose related risks of predisposition to breast carcinoma and thromboembolic disease. However, women who have already sustained bone loss or whose climacteric symptoms are predominantly psychological may require a higher dose of oestradiol, as might those women who continue to experience symptoms, despite 25 mg implants.

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