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The effects of subcutaneous hormone implants during the climacteric

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Climacteric symptoms in 120 women were treated with a total of 469 hormone implants (oestradiol 50 mg and testosterone 100 mg) over a period of four years. All patients with a uterus were given an oral progestogen to prevent endometrial hyperplasia. There was a marked response to treatment, hot flushes being improved in all patients, depression in 99% and loss of libido in 92%. Patient acceptability of this type of treatment was good and there were few side effects or complications.

After therapy, the serum oestradiol exceeded the serum oestrone but remained within normal limits. When climacteric symptoms returned and re-implantation occurred the serum levels of oestrone, oestradiol, luteinising hormone (LH), follicle stimulating hormone (FSH) and testosterone were within the normal range for the reproductive age. This indicates that the return of symptoms is due to a change in the hormone levels rather than absolute hypo-oestrogenism.

(Key words: Climacteric, Hormone implants, Clinical effects, Oestradiol-serum levels)

Introduction

Oestrogen replacement therapy is now accepted as the appropriate treatment for the climacteric syndrome. It is usually administered orally, but this requires daily patient compliance, may produce side effects of nausea and vomiting and does not allow for the use of testosterone, for psychosexual problems, which is hepatotoxic when given orally as methyltestosterone [1].

The use of implants, which release their active components over a period of several months, was first described by Bishop [2] and their use as an alternative treatment for the climacteric syndrome was introduced in 1949 [3]. Despite some early interest [4], hormone implant therapy was not widely used for over twenty years, and although its use was later advocated, especially for castrated women [5], it has not gained the same popularity as oral oestrogen therapy. This is unfortunate because the technique is simple. Hormone pellets can be implanted under local

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anaesthetic as an out-patient procedure [6], and the inconvenience of daily tablet taking is avoided. They also produce a physiological serum oestradiol to serum oestrone ratio greater than unity [7], in contrast to the abnormally high serum oesterone levels produced by most orally administered oestrone or oestradiol [8].

It has been stated that hormone implants should never be used for patients with a uterus [9] but it is our policy to use implants in such patients as first line therapy, particularly in women who complain of co-existent lethargy, depression or loss of libido.

The diagnosis of the menopause is retrospective and some patients may present with symptoms whilst still menstruating whereas others attend up to several years later. The climacteric symptoms of hot flushes, night sweats and vaginal dryness are well defined, but others such as insomnia, depression and psychological problems may be due to other social and family factors operative at this age. In this study, we have divided patients into pre-menopausal and post-menopausal groups to assess any differences in symptom pattern, response to treatment and hormone blood levels following treatment.

Patients and methods

One hundred and twenty women attending the Dulwich Hospital Menopause Clinic for their climacteric symptoms, all of whom had already received at least one hormone implant, were admitted to the study. These patients were consecutive and unselected. They were divided into two groups according to their last pre-treatment menstrual period. Those who had not stopped menstruating or who had had a period within the last 12 mth before treatment was commenced were classified as 'pre-menopausal', and those who had not menstruated for 12 mth before the onset of implant therapy were classed as 'post-menopausal'. Of the 53 women in the pre-menopausal group (A), 7 had undergone a hysterectomy with conservation of the ovaries, within the previous year, whilst still menstruating. There were 67 post-menopausal women (B) of whom 18 had undergone a hysterectomy. The mean age for Group A patients was 44.5 yr (range 35–54 yr) and for Group B patients was 53.3 yr (range 34–71 yr). Oral hormone replacement therapy had previously been prescribed for 66% of Group A patients and 71% of Group B patients. This had proved unsatisfactory in 43 and 51%, respectively. Psychoactive drugs had been used for 51% of Group A patients and 42% of Group B patients, with 41 and 64%, respectively, finding these drugs helpful.

Hormone implants were prescribed for a variety of indications, including unsatisfactory oral therapy, the predominance of psychosexual symptoms (because of the availability of testosterone), convenience following a hysterectomy (because progestogens were no longer required) and patient request. No patient had any contraindication to hormone replacement therapy and all had received between one and six consecutive implants of oestradiol 50 mg and testosterone 100 mg at 4–12 monthly intervals over a period of up to 4 yr.

All patients with a uterus were given norethisterone 5 mg daily for the first 7 days of each month. This regime was only altered if heavy or irregular bleeding was noticed or if endometrial hyperplasia was discovered.

A full history was taken and clinical examination including breasts, abdomen and pelvis was performed prior to hormone administration and on entry into the study. The patient's weight and blood pressure were recorded during each visit and a Vabra curettage was performed (when appropriate) before hormones were prescribed and annually thereafter.

On admission to the study a questionnaire was completed comparing the patient's symptoms before and after implant therapy together with any side effects of treatment. In the majority of patients, symptoms started to recur at approximately 6 mth; at this time, blood was taken for serum hormone estimations (FSH, LH, oestrone and testosterone). All patients chose to continue implant therapy when their symptoms returned.

Results

A total of 469 implants were given, 183 to Group A and 286 to Group B. The duration of symptom relief was 6 mth in 85% of Group A and 69% of Group B (range 3–12 mth for both groups).

The effects of implants on symptoms is shown in Table II. The χ^2 test was used to compare the two groups of patients. A significantly greater proportion of patients in Group B suffered from flushes ($P < 0.03$). There was no significant difference in any of the other symptoms. Log linear models were used to test for differences in the effect of treatment on each symptom; no significant differences were noted.

TABLE I

SYMPTOM RELIEF.

Symptoms	Present (% of patients)		Complete relief (% of patients with symptom)		No relief (% of patients with symptom)	
	Group A	Group B	Group A	Group B	Group A	Group B
Hot flushes/sweats	71.7	89.6	97.4	86.7	0.0	0.0
Headaches	83.0	73.1	65.9	67.3	9.1	4.1
Insomnia	71.7	74.6	63.2	58.0	13.1	10.0
Palpitations	50.9	40.3	55.6	63.0	14.8	7.4
Bone pains	54.7	64.2	55.2	53.5	6.9	11.6
Dyspareunia	45.3	53.7	62.5	77.8	16.7	2.8
Loss of libido	84.9	82.1	66.7	67.3	6.7	10.9
Irritability	90.6	79.1	68.8	77.4	6.3	1.9
Poor memory/concentration	79.2	62.7	59.5	66.7	9.5	7.1
Depression	81.1	77.6	79.1	73.1	2.3	0.0
Lethargy	79.2	73.1	61.9	69.4	4.8	0.0
Urethral syndrome	13.2	26.9	28.6	50.0	28.6	16.7

TABLE II

SIDE EFFECTS OF HORMONE IMPLANTS.

Side effect	Incidence (%)	
	Group A	Group B
Breast discomfort	28.3	17.9
Increased facial hair	22.6	19.4
Acne	5.7	1.5
Abnormal bleeding	16.3	16.4

Changes in systolic and diastolic blood pressure were not significant, nor was weight change in either of the groups. Side effects are shown in Table II. The χ^2 test showed that there was no significant difference between the two groups of patients in the occurrence of side effects due to hormone implants. No patient wanted to stop implant therapy because of the severity of side effects. Abnormal bleeding (in the presence of a normal Vabra curettage) was treated by increasing the duration of norethisterone to 5 mg daily for the first 10 or 13 days of each month. There were no complaints of nausea or vomiting.

No side effects were attributed to the 7 days of norethisterone in 52.2% of Group A and 57.1% of Group B. However, 39.1% of Group A and 34.7% of Group B complained of pre-menstrual tension during progestogen therapy and 17.4% of Group A and 12.2% of Group B suffered from dysmenorrhoea. A log mean model was used to test for differences in the side effects of progestogens; no significant difference was found. The incidence of pre-menstrual tension and dysmenorrhoea were reduced by changing the norethisterone to a 5-day course (if the Vabra curettage was normal) or by halving the dose.

Prior to the index implant two of the pre-menopausal and five of the post-menopausal patients had developed cystic glandular hyperplasia during implant therapy. In all cases this had been corrected by norethisterone 5 mg twice daily for 21 out of 28 days for two cycles [10]. The complications encountered during the study were few. 5.7% of Group A and 3.0% of Group B developed benign breast pathology. Vabra curettage revealed a 5.7- and 6.0%-incidence of cystic endometrial hyperplasia in Groups A and B, respectively. There was one case of deep venous thrombosis in a Group B patient. Fisher's Exact Test showed no difference in the presence of complications in the two groups.

The endometrical histology (from Vabra curettage) on admission to the study is shown in Table III. All patients who developed cystic glandular hyperplasia were also treated with two courses of norethisterone as described above. In all cases the abnormality was corrected and the patient's routine duration of norethisterone increased to 10 or 13 days each cycle. No patient required a hysterectomy for endometrial pathology or heavy uterine bleeding.

Blood hormone levels at six months after varying numbers of implants are shown in Tables IV and V. The serum FSH and LH fell consistently after successive implants, although the levels or oestrone and oestradiol showed little evidence of

TABLE III

ENDOMETRIAL HISTOLOGY.

Endometrium	Group A		Group B	
	n	%	*n*	%
Non applicable	7	13.2	18	26.9
Unsatisfactory	4	7.5	9	13.4
Proliferative	31	58.5	28	41.8
Secretory	8	15.1	8	11.9
Cystic glandular hyperplasia	3	5.7	4	6.0

TABLE IV

GROUP A: HORMONE LEVELS AT 6 MONTHS.

Implant number	1 ($n=10$)	2 ($n=8$)	3 ($n=10$)	4 ($n=8$)	5 ($n=10$)	6 ($n=4$)
FSH (μ/l)	8.1	7.0	4.5	4.8	1.9	1.0
LH (μ/l)	15.4	5.5	6.3	4.6	7.2	0.8
Oestrone (pmol/l)	278	622	401	413	491	722
Oestradiol (pmol/l)	484	748	854	582	828	951
Testosterone (nmol/l)	2.7	2.2	2.7	2.5	3.8	2.6

Normal pre-menopausal values: FSH 1–13 μ/l, LH 1–100 μ/l, oestrone 150–1000 pmol/l, oestradiol 90–1050 pmol/l, testosterone 0.6–2.28 nmol/l.

TABLE V

GROUP B: HORMONE LEVELS AT 6 MONTHS

Implant number	1 ($n=4$)	2 ($n=9$)	3 ($n=12$)	4 ($n=13$)	5 ($n=8$)	6 ($n=14$)
FSH (μ/l)	16.3	17.4	9.3	3.8	5.9	3.1
LH (μ/l)	14.2	14.9	7.9	4.3	4.8	3.6
Oestrone (pmol/l)	353	543	390	470	340	416
Oestradiol (pmol/l)	539	684	860	691	608	704
Testosterone (nmol/l)	2.3	3.1	2.4	3.3	2.6	2.7

Normal post-menopausal values: FSH > 45 μ/l, LH > 30 μ/l, oestrone 37–150 pmol/l, oestradiol 34–220 pmol/l, testosterone 0.55–3.38 nmol/l.

accumulation and did not exceed the normal pre-menopausal range. The oestradiol to oestrone ratio remained greater than unity throughout. Plasma testosterone levels at the time of return of symptoms and re-implantation remained in the upper normal range.

A significant difference ($P < 0.05$) was found in the FSH level between the groups after taking the number of implants into account using covariate analysis. There was no significant difference for the other hormones.

Discussion

Women complain of climacteric symptoms before or for several years after their menopause. Pre-menopausal patients have already been shown to complain of emotional problems more frequently than their post-menopausal counterparts [11]. We would confirm these findings, the proportion of post-menopausal patients complaining of hot flushes being significantly greater than the pre-menopausal group and the number of pre-menopausal women complaining of psychological symptoms being greater than the post-menopausal group, although these did not quite reach significance. We also note that 59.3% of pre-menopausal patients but only 35.7% of post-menopausal patients had found psycho-active drugs helpful for their symptoms.

The FSH level in the pre-menopausal patients with alleged climacteric symptoms was lower than the level found in the post-menopausal patients even after 6 and 12 mth of therapy. This confirms the findings of Chakravarti et al. [12] using oral conjugated equine oestrogens. In spite of this difference the response to oestradiol and testosterone implant therapy was the same.

Loss of libido was a presenting symptom in over 80% of patients in both groups and hormone implant therapy produced a complete cure in two-thirds of the patients. This is an important finding. Studd et al. [11] have shown that psychosexual problems occurring after the menopause respond to testosterone, and as it cannot be administered orally, 6 monthly subcutaneous implantation provides an ideal alternative.

Side effects from hormone implant therapy were few. Although mild breast discomfort was noted by some patients, early in treatment, this always resolved spontaneously and did not prevent any patient from continuing treatment. A 20% incidence of hirsutism may appear alarming but this was no more than a slight increase in downy facial hair elicited on direct questioning and was always improved when the dose of testosterone was halved or discontinued in subsequent implants. Heavy or irregular bleeding was easily controlled by modifying the progestogen regime.

We find that the main problem with implant therapy is the side effects caused by the progestogens. There is a high risk of endometrial hyperplasia in unopposed oestrogen therapy [13] but this can be completely avoided by prescribing progestogens for 10 or 13 days each cycle [10]. We have found that the prescription of progestogens for 7 days/mth is an acceptable compromise. Seven or our 95 patients with a uterus (7.4%) developed cystic glandular hyperplasia which, in all cases, was reversed by long courses of progestogens and did not recur when the duration of the regular monthly course was subsequently increased. It is clear that the protection of the endometrium is related to the duration of progestogen and the troublesome symptomatic side effects a result of an excess daily dose of progestogen.

The only major complication which we felt required cessation of hormone replacement therapy was one case of deep venous thrombosis which occurred in a post-menopausal patient. Because of the increased incidence of deep venous thrombosis amongst oral contraceptive pill users there is anxiety regarding changes

in clotting factors in peri-menopausal patients taking hormone replacement therapy. However, there is no good evidence that healthy post-menopausal women taking oestrogen replacement therapy are at greater risk of developing arteriovenous thrombosis [14], and the results of a large epidemiological study suggest that the real incidence of coronary thrombosis is less than half that of the controls [15]. It is probable that oestradiol does not cause any increase in thromboembolic phenomena, and we found no increase in blood pressure.

It has been inferred that oestradiol is poorly absorbed from the gastro-intestinal tract [16], although more recently it has been shown that an oral preparation containing oestradiol with oestrone and estriol given in high dosage does increase the serum oestradiol level for up to 48 h after ingestion [17]. With subcutaneous oestradiol implants however the serum oestradiol exceeds the serum oestrone from the start of treatment, and as this is the normal ratio in pre-menopausal women it would seem to be preferable to the reversed ratio caused by most oral preparations. In spite of the increasing suppression of FSH and LH with successive implants, there was no evidence of cumulative levels of oestradiol, oestrone or testosterone. But the fact that the serum levels of these hormones were above normal at the time of return of convincing symptoms and re-implantation poses many questions regarding basic endocrinology and the relationship of symptoms to hormone levels. It would seem that these typical climacteric symptoms are due to a change of serum oestrogen and testosterone levels from moderately high levels to normal, rather than a result of low post-menopausal values of oestradiol and testosterone. From this study, we conclude that subcutaneous hormone implants are an effective, acceptable treatment for climacteric symptoms in both pre- and post-menopausal women with few side effects or complications. The presence of a uterus is not a contra-indication as endometrial pathology and irregular bleeding can be prevented or corrected by cyclical oral progestogens for 5-13 days each month.

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