

## TREATMENT OF MENOPAUSAL OESTROGEN DEFICIENCY SYMPTOMS IN HYSTERECTOMISED WOMEN BY MEANS OF 17 $\beta$ -OESTRADIOL PELLET IMPLANTS

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**Abstract.** Ninety-four women having undergone hysterectomy, with or without simultaneous ovariectomy, were treated for menopausal symptoms by means of subcutaneous implantation of sterile pellets containing 20 mg 17 $\beta$ -oestradiol, 589 implantations in all. The subjective effect was good and lasted generally for about 6 months. The Karyopyknotic index, serum FSH and plasma oestradiol were checked in a few of the patients. The method was judged to be valuable in appropriate cases.

17 $\beta$ -oestradiol—the most important of oestrogens occurring naturally in man—has long been used for treating menopausal symptoms, in the form of esters for injection and, in recent years, for oral use in esterified and free forms (1, 3, 4, 6, 8, 10). The use of oestradiol in the form of pellets for subcutaneous implantation is not new. In particular, before long-acting oestradiol esters for injection became available, this method was used to a certain extent, but only on a small scale. There are only brief references to it in the literature. The author was able to find only one more comprehensive study—that of Müller (9). Chlorinda et al. (2), Stallworthy (13), Schleyer-Saunders (11) and Studd (14) mention the method without giving details of the patient sample. The patients in Müller's investigation were mostly women with intact wombs. According to present knowledge of oestrogen treatment it is not surprising that bleeding occurred fairly frequently. The method is scarcely suitable for patients with uterus intact. Even with small amounts of oestrogens, bleeding readily occurs if the treatment is administered continuously for a long time. Furthermore continuous oestrogen treatment may possibly predispose patients to endometrial cancer. The implantation method should therefore be reserved for women who have undergone hysterectomy. The author has used the

method on such patients for more than 20 years. The preparation used—Dimenformon compr. ad implantationem (depot tablets)—was formerly registered in Sweden but over the last 10–15 years has been obtainable for licensed trial by courtesy of N/V Organon. The sample discussed in this paper comprises all patients who have been accepted for treatment during the ten years from 1965 to 1975.

### METHOD

The preparation consists of compressed rod-shaped pellets containing 20 mg 17 $\beta$ -oestradiol without excipient. The pellets measure 2 mm in diameter and are 6 mm long. Each pellet is packed sterile in a vial. Their shape makes it easy to implant the pellet subcutaneously using a trocar and cannula. It also means that the surface area and therefore the absorption rate vary little during absorption period.

Implantation is effected with a cannula with the same inside diameter as the diameter of the pellet implant (2 mm) and provided with two trocars—one pointed for introducing the cannula and one blunt for inserting the pellet. The implantations were effected subcutaneously in the lower abdominal wall. The technique is extremely simple. After a little local anaesthetic has been injected intra- and subcutaneously, a small incision, 1–2 mm long, is made through the skin with a pointed scalpel blade. Through this the cannula with the pointed trocar is inserted 5–8 cm in the subcutaneous fat, nearly parallel to the skin, after which the implant pellet is inserted into the cannula and pushed in with the blunt trocar. No suture is required. With a little practice the whole procedure takes less than half a minute. No visible scar is left. Only at one single implantation did bleeding necessitate a suture. Occasionally minor, insignificant haematomas have appeared, but never any infection or other complication. Any discomfort is insignificant and patients who have also had hormone injections report that the implantations are less unpleasant than injections. When implanting in conjunction with laparotomy, the pellet may be inserted from the operation incision with a pair of tweezers into the subcutaneous fatty tissue.

Table I. *Duration of the effect on climacteric symptoms*

| Duration (months) | No of implant. | % of implant. with duration indicated (508) |
|-------------------|----------------|---------------------------------------------|
| 0-4               | 2              | 0.4                                         |
| 4-5               | 19             | 3.7                                         |
| 5-6               | 104            | 20.5                                        |
| 6-7               | 254            | 50.0                                        |
| 7-8               | 49             | 9.7                                         |
| 8-                | 80             | 15.7                                        |
| Undefined         | 81             |                                             |
| Total             | 589            | 100                                         |

### PATIENTS

The series consist of 94 patients, all of whom had undergone hysterectomy—in most cases total—including 46 with simultaneous bilateral ovariectomy. For 15 of the patients, the first implantation was effected in conjunction with the operation, for the others from less than 1 year to 29 years afterwards. The ages at the start of treatment ranged from 38 to 72.

The indications for treatment were, in the first instance, typical menopausal disorders in the form of sweating and hot flushes. Less continuous symptoms such as headache, palpitation, muscular pains, insomnia and various mental symptoms often occurred simultaneously. In some older patients the symptoms of sweating and hot flushes were insignificant or completely absent. The indication for treatment was here primarily urogenital symptoms such as vaginal atrophy with symptoms of so-called senile colpitis, dysuria and urgency incontinence, together with difficulties in resuming sexual relations. Even in milder cases of stress incontinence, the treatment was of some value.

The series includes altogether 589 implantations. The number of implantations in cases where the effect could be studied was between 2 and 38—for 61 patients at least 5 and for 26 patients at least 10 implantations.

### RESULTS

The assessment of the effect was based primarily on information given by the patients themselves. The subjective effect was very good throughout. Only 2 patients reported an unsatisfactory effect on sweating and hot flushes. Many patients had previously various forms of oestrogen treatment and practically all preferred the implantation method. The patients also included an appreciable number who had previously been treated with sedatives and similar preparations without any effect whatsoever. It is often stated that the placebo effect when treating menopausal symptoms is high. Figures up to 35% have been indicated (5). This does not tally

with the author's own experience, nor with more recent investigations. Lauritzen (6) indicates a figure of 10–13%. The very poor effect of sedatives in itself constitutes evidence against a very high degree of placebo effect.

No direct comparison with placebo could be made in the present investigation, though some efforts in this direction were made, however. Thus when implantation was effected at the same time as a bilateral ovariectomy, the patients were not informed about implantation but were asked to report if any climacteric symptoms appeared. The duration of effect for this first implant is the same as that for the patients as a whole. The mean duration for implantation in conjunction with operation was  $5.9 \pm 0.03$  months. For all cases together it was  $6.1 \pm 0.05$  months. Difference  $0.2 \pm 0.3$  months.

Presumably the absorption time would be curtailed if the pellet was fragmented, and this was, in fact, observed when it was unintentionally broken during implantation. This seemed to afford a chance to determine to what extent the patient's idea of the effective duration might be influenced by the check-up being usually arranged for 6 months later. In 21 cases selected at random, the pellet was deliberately broken into 2–3 pieces before being implanted. This was not recorded in the notes, so that the doctor should not unintentionally lead the patient when asking about the duration of the effect. The notes concerning fragmentation were not taken out until we went through the material for processing it. This showed, as anticipated, that the interval before the disorders returned was, indeed, shorter than usual. It varied between 4 and 6 months with an average of  $5.2 \pm 0.15$  months compared with  $6.1 \pm 0.05$  months for the whole sample. The difference was  $0.9 \pm 0.16$  months and therefore statistically significant.

Table I shows the duration of the subjective effect. As a rule the patients were treated again after 6 months. This period was modified in individual cases according to the duration of the effect. The patients were requested to note the time of onset of sweating and flushes and were usually given a prescription for some oral oestrogen preparation to take when necessary. Only in exceptional cases did they need to avail themselves of this. The effective durations indicated in the table are to be regarded as minimum ones as those patients who, upon return and further implantation, had not always had a recurrence of symptoms at that time. Thus "6–7

Table II. *Objective parameters*

| Determin.         | Before treatment |               |                 | 3 months |               |                  | 6 months |               |                  | Months Difference |                                                        |
|-------------------|------------------|---------------|-----------------|----------|---------------|------------------|----------|---------------|------------------|-------------------|--------------------------------------------------------|
|                   | No.              | Vari-<br>tion | Mean            | No.      | Vari-<br>tion | Mean             | No.      | Vari-<br>tion | Mean             |                   |                                                        |
| K1, %             | 6                | 0-10          | 2.0             | 6        | 35-66         | 46.1             | 6        | 10-40         | 18.5             | 0-3<br>0-6<br>3-6 | 44.1 ***<br>16.5 **<br>-27.6 **                        |
| FSH,<br>$\mu$ g/l | 5                | 6.7-15        | 10.5 $\pm$ 1.7  | 10       | 0.4-9.2       | 3.7 $\pm$ 1.0    | 16       | 0.5-14        | 4.1 $\pm$ 0.8    | 0-3<br>0-6<br>3-6 | 6.8 $\pm$ 2.0<br>6.4 $\pm$ 2.4<br>0.4 $\pm$ 1.3        |
| E2, pmol/l        | 3                | 37-92         | 56.3 $\pm$ 21.8 | 7        | 69-330        | 195.1 $\pm$ 34.1 | 15       | 59-242        | 152.5 $\pm$ 14.7 | 0-3<br>0-6<br>3-6 | 138.8 $\pm$ 40.5<br>96.2 $\pm$ 26.3<br>42.6 $\pm$ 37.1 |

\*\* *t*-Test  $p < 0.05$ . \*\*\* *t*-Test  $p < 0.005$ .

months" means at least 6 months but may exceed 7 months. If symptoms had not recurred at two consecutive implantations, the time for check-up was postponed by one month. If there were no symptoms even then, the treatment was concluded, to be resumed when necessary. "0-4 months" means that the effect had a duration of less than 4 months or was incomplete. The title "undefined" indicates cases where it was not possible to judge the effective duration more accurately—chiefly patients with virtually only urogenital symptoms. The table shows that in a large majority of cases a completely satisfactory effect was obtained for about half a year. Individual variation was rarely more than 1 month except in cases with fragmentation of the pellet. On the other hand, some patients consistently requested rather more frequent implantations than did others. It is remarkable how accurately the patients could detect the time of return of the symptoms, as a rule within one or two weeks.

In order to gain a more objective idea of the hormone effect, objective parameters were used for smaller groups of the sample. Thus we studied the karyopyknotic index, serum FSH, and plasma oestradiol. Estimation of FSH and oestradiol was generally performed 3 and 6 months after implantation. The results are given in Table II. For 3 patients more detailed studies were carried out in conjunction with the first implantation. In these cases FSH and oestradiol were determined immediately before implantation and then after 1 week, 2 weeks and 1, 3, 5, 6 and 7 months (Fig. 1).

For 6 patients, even at the first implantation, the karyopyknotic index was determined before implantation and again after 3 and 6 months (Table II).

As shown by Fig. 1 the oestradiol levels rise and the FSH starts to fall within one week, which tallies well with the patients' own statements about the disappearance of the climacteric symptoms. The levels then remain fairly constant for up to about 5 months. By 6 months the levels have regained or begun to approach the original levels.

Plasma oestradiol and serum FSH were determined by radioimmunoassay (15). The upper limit for FSH in women of childbearing age is 3  $\mu$ g/l. Postmenopausally the values range from 5  $\mu$ g/l upwards.

The karyopyknotic index started to fall at 6 months but, in none of the 6 cases studied was it as low at 6 months as at the beginning of treatment.

The FSH and oestradiol values at 6 months had by no means always returned to the original levels. The quickest to react is plasma oestradiol, as is to be expected, since this is the primary parameter. It is also the one which best corresponds to the return of menopausal symptoms. As a rule, menopausal symptoms return when the plasma oestradiol falls below 100-120 pmol/l. Serum FSH certainly gives a good idea of the effect of an oestrogen but need not necessarily drop despite a good effect of treatment. This seldom occurs, however, and, in fact, did not do so for any of the patients studied in the present sample. For one patient, however, the drop in FSH, was appreciably less than usual 15, 9.2, and 14  $\mu$ g/l at 0, 3, and 6 months respectively. Despite this, the effect was very good and the disorders had not returned after 6 months. On the other hand, the one and only patient whose plasma oestradiol did not reach 100 pmol/l after 3 months was one of the two cases where the effect was unsatisfactory. Unfortu-

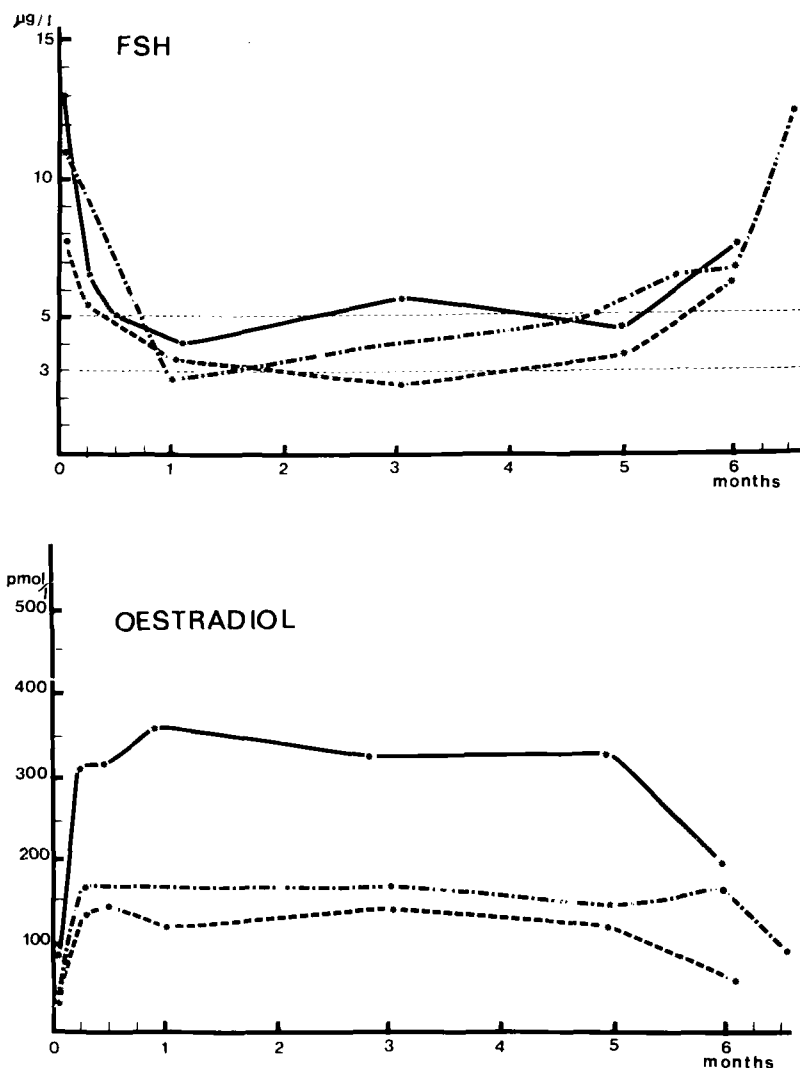


Fig. 1. Serum FSH and plasma oestradiol after subcutaneous implantation of 20 mg 17 $\beta$ -oestradiol after the first implantation in 3 cases.

nately, oestradiol determination was not carried out for the second of these patients.

The appearance of the vaginal epithelium and the vaginal and—when cervix was left—the cervical secretion also showed a picture of strong oestrogenic influence.

#### SIDE EFFECTS

*Mastalgia* was reported by 4 patients, all over the age of 60. Only one of them regarded it as severe enough to want to switch to different treatment. Otherwise, no side effects were reported.

Since all patients had undergone hysterectomy,

no bleeding could occur. Likewise, endometrial cancer does not of course come into the picture. There were no cases of mammary or ovarian cancer, nor of thrombosis. In all, the investigation covered approximately 300 patient-years.

Treatment was *discontinued* for 10 patients: in one account of mastalgia (changeover to week oral oestrogen treatment) and in 2 due to lack of effect. In one of these the patient was switched over to oestrogen injections, in the other to high oral doses of oestradiol. Three patients stopped treatment because they felt that they no longer needed oestrogens and 4 changed over to oral treatment on practical grounds.

## DISCUSSION

The most important of the natural oestrogens in man—17 $\beta$ -oestradiol—has proved to be extremely useful for treating menopausal symptoms both at oral and parenteral administration. With oral treatment, the doses must, however, be kept considerably higher than for alkylated oestrogens, e.g. ethinyloestradiol. On the other hand, many studies (1, 3, 6, 7, 16 etc.) have demonstrated advantages compared with these, chiefly as regards the effect on blood lipids, osteoporosis and the coagulation system.

The method described here—subcutaneous implantation of 17 $\beta$ -oestradiol in the form of sterile pellets—is not suitable as a general oestrogen treatment because the absorption time is too long to allow of the requisite breaks in the treatment at 1–2 monthly intervals. However, this does not seem likely to be a drawback for a patient whose uterus has been removed. In such circumstances the very long duration affords considerable advantages. It is virtually always possible to achieve a wholly satisfactory effect with two implantations per annum. The method is simple and is preferred by many patients to other methods of administering oestrogens. It is remarkable that such small amounts of oestrogen are required to keep the patients free of symptoms. With an effective duration of 6 months, the daily dose of oestradiol can be calculated to approximately 0.1 mg compared with about 0.3 for injections of long-acting oestradiol esters and at least 1 mg with oral administration of oestradiol or oestradiol esters. If the postmenopausal endogenous production of oestradiol is reckoned at about 80  $\mu$ g/24 h (12), the method would afford a total amount of oestradiol of nearly 200  $\mu$ g/24 h, which corresponds closely to normal oestrogen production in the years before the menopause (5). The relatively low but constant oestrogen level may be the reason for many patients finding that they feel better with the implantation treatment than on oestrogens otherwise administered. The effect is nearly always complete, whilst on the other hand sign of too high oestrogen level, such as mastalgia and oedema, occur only in quite exceptional cases.

The disadvantage, of course, is that the method involves seeing a doctor. However, the time involved in the treatment is very short. The implantation method seems to be particularly valuable in bilateral ovariectomy. We can thereby completely

obviate the often very severe oestrogen deficiency symptoms which are the immediate sequelae of the operation—an added strain in the postoperative condition of stress experienced by the patient.

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