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Oestradiol and testosterone implants

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Hormone implantation is a physiological delivery system for oestradiol, and if necessary testosterone, which is long-acting and has the convenience of 6-monthly treatment, and excellent compliance. It achieves higher levels of oestradiol than any other method of administration, and by avoiding first-pass hepatic metabolism minimizes prothrombotic effects upon the clotting system and other potentially adverse metabolic effects. It is a particularly valuable method of oestradiol administration in the following cases: post-hysterectomy; for those with severe climacteric syndrome, especially when depression is a prominent feature; for disorders associated with cyclical ovarian function such as premenstrual syndrome (PMS) and menstrual migraine; to achieve the maximum protective effect upon the skeleton, even in women with established osteoporosis. The addition of testosterone is helpful for women with loss of libido, loss of energy, depression and headache which have not adequately responded to oestrogens alone.

In spite of many apparent advantages over other routes, hormone implants are only licensed in a few parts of the world. It is perhaps seen as an aberration of English-speaking societies, along with cricket and boarding schools, as enthusiasts are found in the United Kingdom, Australia, South Africa and the United States which has 200 licensed users. This is hard to understand because hormone implants are, in our view, the straightforward treatment of choice in many conditions, particularly in the woman without a uterus. The pharmacokinetic and metabolic effects of implants have been extensively reviewed (Studd and Magos, 1986; Magos and Studd, 1990) and will only briefly be discussed here. More attention will be given to new data relating to premenstrual syndrome, depression, osteoporosis and the side-effects of implantation therapy.

HISTORY

The first record of an implant being given was from Bishop at Guy's Hospital, London in 1938. He described the case of a 20-year-old woman following bilateral oophorectomy with severe menopausal symptoms and use of an implant of 14 mg oestrone. The real pioneer of implant therapy was, however, Greenblatt whose first publication (Greenblatt and Suran,

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1949) described the use of crystalline pellets of oestradiol and testosterone for the treatment of the climacteric syndrome, uterine hypoplasia, dysmenorrhoea and reduced libido. Later he extended the indication for oestradiol implants by describing them as anovulatory, and therefore contraceptive (Greenblatt et al, 1977). Although implants have not found a place in routine family planning, the ability to suppress ovulation has been used as the basis of the treatment of premenstrual syndrome and menstrual migraine (Magos et al, 1983, 1986a). In the United Kingdom, Schleyer Saunders (1974) was an early enthusiastic exponent of implant therapy, and Studd (1979a) has argued that the hormonal profiles achieved and the efficacy of implant therapy suggest that in many patients with severe menopausal problems or hormone responsive depression, implants should be used as a first line therapy. For almost 30 years oestradiol implants have been used regularly after hysterectomy in many centres. Both Hunter et al (1973) from Oxford and Lobo et al (1980) from Los Angeles have reported upon their long experiences.

IMPLANTS

In spite of new methods of non-biodegradable implants currently used for contraception, the technology and preparation of implants used for the menopause and premenstrual syndrome have been virtually unchanged over 40 years. Only the method of sterilization has changed. Essentially they are fused white crystalline pellets of the three major sex steroids, 17β-oestradiol, testosterone and progesterone, which are chemically identical to the naturally occurring endogenous hormones. They are manufactured in the United Kingdom by Organon Laboratories and in the United States by Barter Laboratories. They are small slender cylindrical pellets 2.2 or 4.5 mm in diameter, and 3 to 6 mm in length, the surface area determining the rate of oestrogen delivery. The pure hormone is suspended in a cholesterol base, and the pellets are individually packaged in glass vials sterilized by irradiation.

17β-Oestradiol

Oestradiol pellets in the UK are available in 25, 50 and 100 mg sizes, with the usual menopausal dose being 50 mg every 6 months. For premenstrual syndrome the initial dose is usually 75 or 100 mg, reducing in a stepwise fashion by 25 mg every 6 months until a maintenance dose of 50 mg is achieved. For the treatment of established osteoporosis a dose of 75 mg should be used initially.

Testosterone

Unlike the 17-alkylated oral testosterone which is hepatotoxic and icterogenic, an implant of the pure hormone is safe and is the route of choice for repeated administration of androgens. Pellets of 100 and 200 mg are available from Organon and 75 mg from Barter. Treatment is rarely compli-

cated by any excess hair growth, acne or other signs of virilization. Voice change does not occur.

Progesterone and progestogens

Natural progesterone and the 19-nor-steroid derivatives, norethisterone and levonorgestrel are available as subdermal implants and have been advocated for contraception and for the treatment of premenstrual syndrome. They frequently cause a chemical reaction at the site of implantation and as there is no evidence that progesterone is effective in the treatment of premenstrual syndrome, and as their manufacture by Organon will soon be discontinued, they will not be discussed further.

Technique of hormone implantation

The technique of hormone implantation has been described in detail by Thom and Studd (1980). It is an easy, quick and safe office procedure carried out under local anaesthesia (Figures 1 and 2). Although a no-touch technique is used it is nowadays desirable to wear gloves routinely in order to avoid blood contact.

The implants are usually inserted into the subcutaneous fat of the lower abdominal wall or into the fat of the upper outer quadrant of the buttock. The skin is cleansed with antiseptic and a track of tissue anaesthetized with 1% lignocaine with adrenaline. A 5 mm incision is made in the skin and a trochar especially designed for the purpose is pushed through the incision up to the hilt into the fat. The rectus sheath and underlying muscle and any

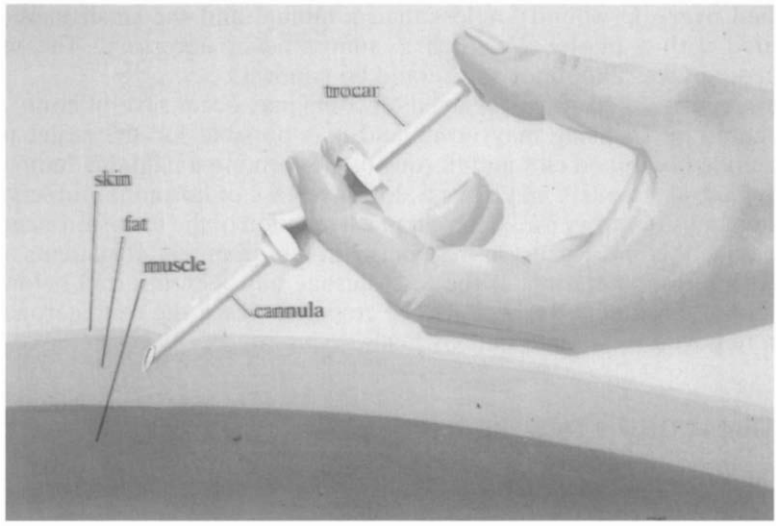

Figure 1. Hormone implant introduced into subcutaneous fat via trocar and cannula.

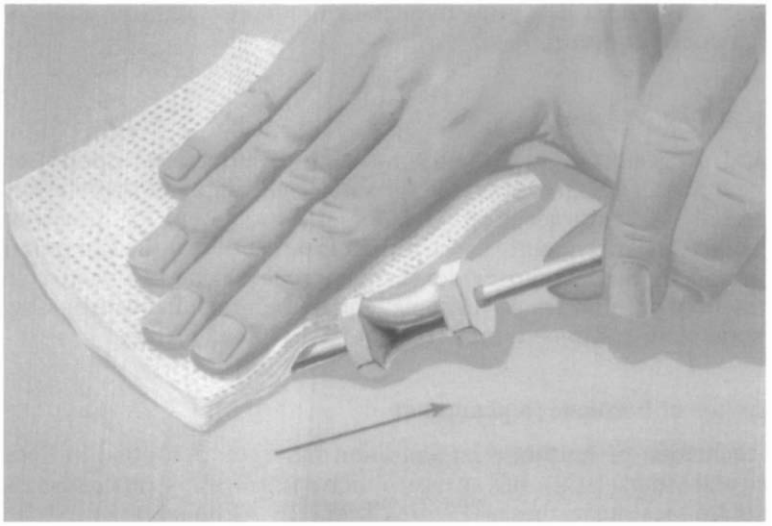

Figure 2. Light pressure applied for few minutes; no suture required—simple elastoplast dressing.

adjacent scar should be avoided as this is likely to produce pain and bleeding.

The pellets are emptied into a small gallipot which is held under the cannula as they are inserted by means of forceps into the barrel of the cannula. The blunt obturator is inserted into the trochar pushing the pellets into the subcutaneous tissue. The instrument is withdrawn, pressure is applied over the wound for less than a minute and the small incision is covered with a plaster. A stitch is almost never necessary. The whole procedure takes 2 minutes and should be painless.

Complications are rare. Delayed bleeding may occur several hours after implantation. Bruising may occur and it is possible for the pellet to be surrounded by blood clot and fibrous tissue forming a palpable lump. It is likely that such pellets may have a slower release of hormone. Infection of the implant site is very rare but a chemical reaction to the testosterone pellet with rejection and extrusion may occur in less than 1% of patients some weeks after implantation. If the testosterone has been inserted below the oestradiol these pellet(s) will also be rejected. Once the testosterone has been removed the wound quickly heals.

PHARMACOKINETICS OF IMPLANTS

For details of the absorption, metabolism, excretion, metabolic changes and the effects upon pituitary and ovarian function the reader is referred to the extensive review of Magos and Studd (1990). There are, however, some important points to be reviewed here. Thom et al (1981) determined the

concentrations of oestradiol, oestrone and FSH achieved following single implantations of 50 mg and 100 mg oestradiol in postmenopausal women. These data are presented graphically in Figures 3 and 4. There is a rapid rise in oestradiol concentration, and decline in that of FSH, immediately after implantation, with levels peaking at 2–4 months and then declining more gradually. The average levels achieved over 6 months are greater than those achieved with any other mode of administration, but remain well within the

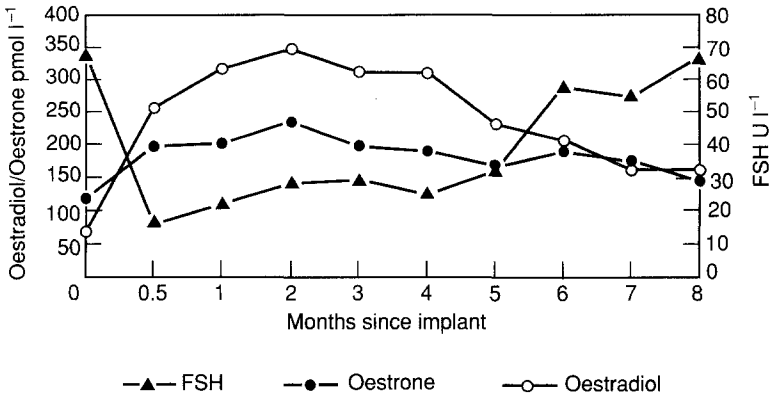

Figure 3. FSH, oestrone and oestradiol concentrations with 50 mg oestradiol implant (from Thom et al, 1981).

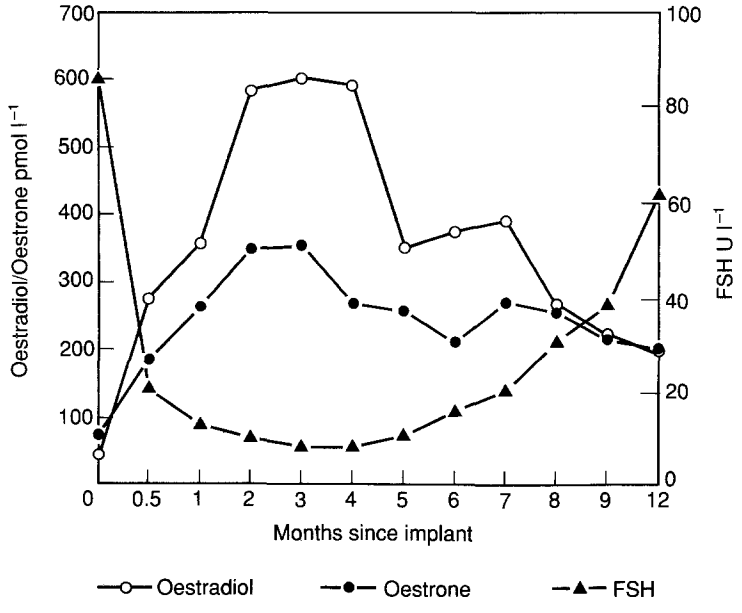

Figure 4. FSH, oestrone and oestradiol concentrations with 100 mg implant (Thom et al, 1981).

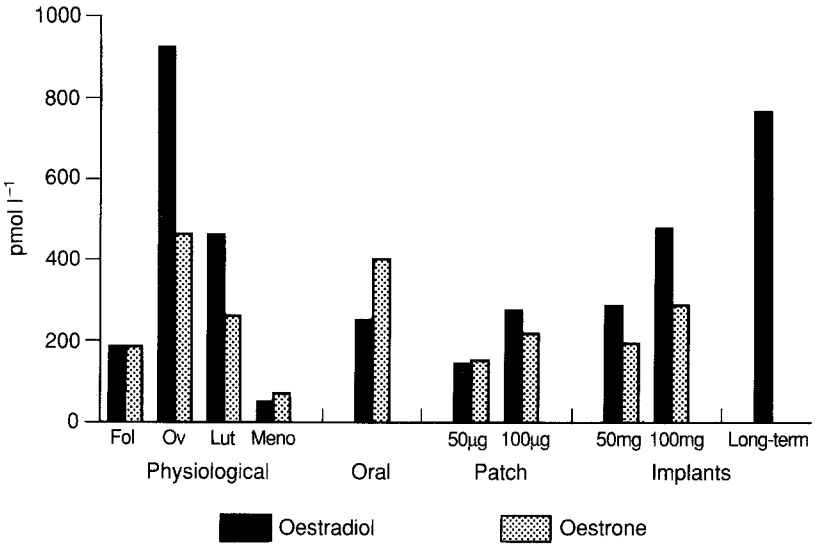

Figure 5. Mean hormone concentrations achieved with different routes of oestrogen delivery (Englund et al, 1977, 1978; Thom et al, 1981; Powers et al, 1985; Garnett et al, 1990; Stanczyck, 1991). Fol, Follicular; Ov, Ovulatory; Lut, Luteal; Meno, Menopausal.

normal physiological premenopausal range (Figure 5). It is also apparent that by the time symptoms usually recur and a repeat implant is given the oestradiol levels are still above baseline (Barlow et al, 1986). This observation has two main sequelae. Firstly that oestradiol implants have a prolonged duration of action. This is well documented; for example, Hunter et al (1973) reported that FSH levels were still depressed up to 3 years after implantation of 100 mg of oestradiol. The second result is that successive implants have a cumulative effect. Again this is well documented by Garnett et al (1990), who found a mean oestradiol level of 767 pmol l^{-1} in 1388 women receiving long-term implant therapy.

Rather than this being a problem it is the mechanism whereby therapeutic oestradiol concentrations in the upper physiological range are achieved. As will be discussed later, supraphysiological levels may occur, usually as a result of repeat implants being demanded and given at increasingly short intervals, but this can be avoided in routine clinical practice by stepping down the dose of implant. Thus although doses of 75 or 100 mg are used initially, the dose should be reduced to a maintenance level of 50 or even 25 mg during the first few years of therapy (Studd et al, 1987). When given in this manner using the correct dose, Cardozo et al (1984), although finding a gradual increase in oestradiol levels with time, did not observe any instances of supraphysiological concentrations.

Two other observations are pertinent. Firstly that implants recreate best the physiological premenopausal 1:1 to 2:1 ratio of oestradiol to oestrone. Although the 100 μg transdermal patch achieves a ratio of 1.2:1, a 100 mg oestradiol implant consistently maintains a ratio of 1.7:1 (Thom et al, 1981;

Powers et al, 1985). Secondly that implants achieve more stable hormone levels than any other mode of administration. Oral therapy leads to very unstable levels: a large bolus of oestrogen, predominantly oestrone in high concentration (up to 1725 pmol l^{-1}), appears in the systemic circulation within hours of ingestion, after which concentrations rapidly decline (Yen et al, 1975). Although transdermal patches are better, oestradiol levels may still vary by more than 150% during the 3–4 day lifetime of a single patch (Powers et al, 1985). By contrast, the day-to-day oestradiol concentrations achieved with implants are remarkably constant (Stanczyck et al, 1988) (Figure 6).

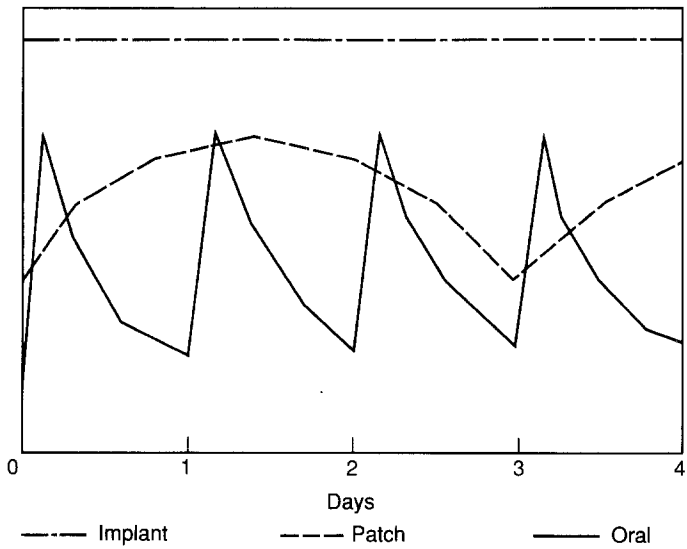

Figure 6. Short-term variation in oestradiol concentrations with oral, patch and implant therapy.

Thus, oestradiol implants may be considered the most physiological method of oestradiol delivery currently available. They avoid first-pass hepatic metabolism, more closely recreate the physiological oestradiol to oestrone ratio, and more consistently achieve premenopausal oestradiol concentrations than other therapies.

There are comparatively little published data concerning the effects of testosterone implants on plasma hormone concentrations and symptoms. Thom et al (1981) showed a fivefold increase in plasma testosterone following a 100 mg testosterone implant, peak levels occurring at 1–2 months, followed by a decline, with a return to pretreatment values at 5 months, ahead of the comparable peak and decay of oestradiol levels following oestradiol implantation (Figure 7).

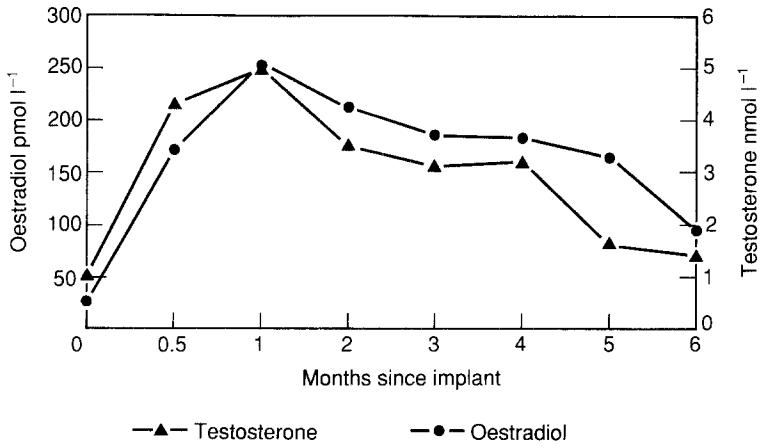

Figure 7. Hormone concentrations after implantation of oestradiol 50 mg and testosterone 100 mg (Thom et al, 1981.)

INDICATIONS FOR IMPLANT THERAPY

Climacteric syndrome

Hot flushes, night sweats and vaginal dryness are the best characterized symptoms of the menopause (Utian, 1972). Although some women may traverse the climacteric without symptoms, the majority will not. Eighty percent will experience hot flushes. In these women flushes occur daily or more frequently in 70%, lead to embarrassment in 70%, cause acute physical discomfort in 50%, and persist for more than 5 years in 25% (McKinley and Jeffreys, 1974). The declining oestrogen levels of the climacteric are also thought to give rise to a variety of other symptoms, collectively referred to as the climacteric syndrome, namely insomnia, depression, headaches, dyspareunia, loss of libido, generalized aches and pains, poor concentration, irritability, poor memory, anxiety and urinary frequency (Brown, 1977; Studd et al, 1977a; Bungay et al, 1980).

While all these symptoms clearly respond to oestrogen replacement (Campbell and Whitehead, 1977; Studd et al, 1977a), the precise relationship between oestradiol levels and symptoms in the case of implant therapy is of interest. Cardozo et al (1984) demonstrated that in the majority of patients receiving implants, symptoms recurred approximately 6 months after the previous implant (range 3–12 months), and oestradiol concentrations at this time remained within the premenopausal range. This leads to the hypothesis that occurrence of climacteric symptoms is not dependent on the absolute concentration of oestradiol or FSH, but rather upon a declining hormone level. Brincat et al (1984) went on to demonstrate that repeat implants relieved symptoms whereas placebo implants did not, giving

further support to the concept that change in oestradiol level is the important variable. In addition they found that the start of appreciable benefit, maximum benefit, start of decline and time of wearing off of the implants, all bore a temporal relationship to the pharmacokinetic profile previously described (see Table 1 and Figures 3 and 4).

Table 1. Relationship between therapeutic benefit and time since implantation of oestradiol.

	Mean (+ or − SEM)
Start of appreciable benefit	2.1 (0.1) weeks
Maximum benefit	5.2 (0.4) weeks
Start of decline	2.5 (0.3) months
Implant wore off	6.4 (0.2) months

Premenstrual syndrome

The disorder of premenstrual syndrome is a complex mixture of endocrine-related changes and a personality/psychiatric disorder. The amount of overlap if any in an individual woman is variable, but the endocrinological aspect of the disease is susceptible to hormonal manipulation. The essential point is that whatever the specific cause of PMS, cyclical ovarian function is a central and necessary feature of the disorder, and therefore suppression of the cyclical hormonal changes of the ovarian cycle by oestrogen is a rational method of treatment (Studd, 1979). This has been successfully achieved in randomized, placebo-controlled trials using oestradiol implants (Magos et al, 1986a), as well as oestradiol patches (Watson et al, 1989). Magos has reported a decrease in ovarian activity using 100 mg oestradiol implants (Magos et al, 1987) with complete suppression of ovarian activity and anovulation from the time of the second 6-monthly implant. In clinical trials oestradiol implants achieved a symptomatic improvement, significantly greater than placebo, in every PMS symptom cluster of the Moos menstrual distress questionnaire, including depression, irritability, headache, bloating, mastalgia and poor work performance (Figure 8). While promising results have been obtained with other anovulatory therapies, such as danazol and luteinizing hormone releasing hormone agonists, neither of these therapies is suitable for long-term use.

A problem with oestradiol implant therapy for PMS is the reappearance of PMS-like symptoms in association with cyclical progestogen. Initial management of this problem is to try different progestogens. Norethisterone 5 mg, dydrogesterone 10 mg and medroxyprogesterone acetate 5 mg daily are all suitable. The next step is to reduce the number of days for which the progestogen is taken, although this should not be reduced below seven per month. In this way a tolerable regimen can be found for most patients, nevertheless 10% of women on long-term therapy will eventually have a hysterectomy because of such progestogenic symptoms (Watson et al, 1990).

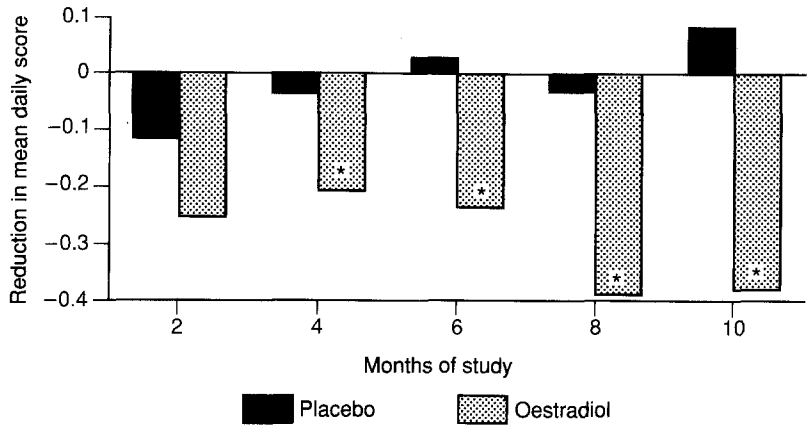

Figure 8. Reduction in total PMS symptom score with oestradiol 100 mg implants. Significantly different from placebo at $p<0.05$. (Magos et al, 1986).

Loss of libido

Against the background of a general decline in sexual activity with advancing age (Kinsey et al, 1953), there is a marked and sudden reduction at the time of the menopause (Pfeiffer et al, 1972; McCoy and Davidson, 1985). That this constitutes a problem is highlighted by the finding that approximately 45% of women attending a menopause clinic will complain of sexual dysfunction (Studd et al, 1977b). While this may be secondary to factors such as vaginal dryness, insomnia associated with night sweats, or concurrent psychosocial stress, it seems that in some women the menopause is associated with a primary loss of libido (Studd and Parsons, 1977).

The precise role of the sex steroids in regulating human female sexuality remains controversial. In healthy premenopausal women there is little evidence to suggest a relationship between plasma oestradiol concentrations and sexual activity (Sherwin et al, 1985), and in the postmenopause although oestrogen replacement may undoubtedly enhance sexual activity by relieving vaginal dryness, it does not appear to effect sexual desire (Coope, 1976; Campbell and Whitehead, 1977; Sherwin et al, 1985). In general, basal testosterone levels are not related to coital frequency. Morris et al (1987), however, found a significant positive correlation between mid-cycle peak testosterone concentrations and frequency of intercourse in healthy, spontaneously-cycling, premenopausal women; Bancroft et al (1991) found a correlation between testosterone levels and coital frequency in healthy, premenopausal, oral contraceptive users. These data suggest that androgens may influence sexual desire in premenopausal women. When one considers that androgen levels drop during the climacteric to approximately 50% of

premenopausal values, it seems logical that androgens should be used to treat menopausal loss of libido. Early controlled trials were very encouraging. Studd et al (1977b) found that combined implants of oestradiol 50 mg and testosterone 100 mg produced a significant improvement in libido in 80% of patients. This work was later confirmed by Brincat et al (1984).

The effects of testosterone were, however, questioned by Dow et al (1983) in a good, placebo-controlled trial. This latter study may be criticized in that the patients studied did not specifically complain of loss of libido. Subsequent work has to a point clarified the issue. Burger et al (1987) clearly showed that combined oestradiol and testosterone implants were significantly superior to oestrogen implants alone in increasing libido in menopausal women with a specific complaint of loss of libido. Similarly, using injectable hormones in women undergoing a surgical menopause, Sherwin et al (1985) clearly demonstrated that testosterone, even when given without oestrogen, improved sexual desire whereas oestrogen alone did not. On balance the conclusion is that testosterone implants are an effective treatment for menopausal loss of libido when this is a specific complaint. They should be given at 6-monthly intervals in conjunction with oestradiol.

Menstrual migraine

Migraine is a common disorder affecting 19% of women. The fact that attacks usually commence after puberty and in 60% headaches are related to menstruation suggests that ovarian hormones may be involved. It is postulated that hormone withdrawal prior to menstruation is the trigger. This is confirmed by the study of Magos et al (1983) in which menstrual migraine responded to the administration of oestradiol implants. These were given in anovulatory doses, and stopped headaches completely or almost completely in 83% of women.

Osteoporosis

Oestrogens are the cornerstone of prevention and treatment of osteoporosis. The reported increases in bone density achieved with oral therapy vary considerably, with most studies finding an increase equivalent to 1% per annum (Lindsay et al, 1976; Christiansen and Christiansen, 1981). Transdermal patches appear more potent, achieving a 3.5% increase in vertebral bone density over 12 months (Stevenson et al, 1990). If the skeletal response is related to the oestradiol dose administered it might be expected that implants may be a more effective way of preventing osteoporosis. Savvas et al (1988), in a cross-sectional study of women having had 8 years of oestrogen therapy, showed greater values for spine and proximal femur bone density in patients receiving implants than those on oral therapy. They suggested that this may be due to a difference in oestradiol levels as the median oestradiol concentration was 725 pmol l^{-1} (range 372–2370 pmol l^{-1}) and median FSH was 1 IU l^{-1} (range 1–11 IU l^{-1}) in the women receiving implants whereas the respective values for women taking conjugated equine oestrogen were 170 pmol l^{-1} (range 30–651 pmol l^{-1}) and 43 IU l^{-1} (range 4–94 IU l^{-1}).

Later, a prospective study of 23 postmenopausal patients, using dual photon technology, showed an 8.3% increase in spinal bone density and a 2.8% increase in that of the hip after 1 year of oestradiol 75 mg and testosterone 100 mg implants (Studd et al, 1990) (Figure 9). The incremental increase in vertebral and femoral bone density was significantly correlated

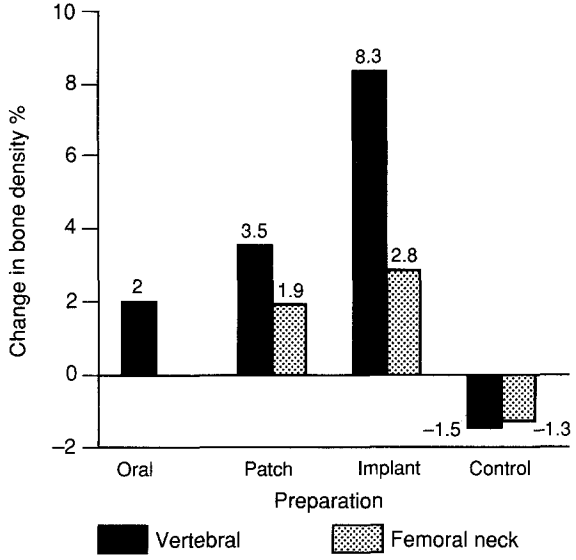

Figure 9. Increase in bone density achieved with different routes of oestrogen administration. Implant, 75 mg; patch, 50 μg; oral, oestradiol. (Christiansen et al, 1981; Lindsay et al, 1976; Stevenson et al, 1990; Studd et al, 1990.)

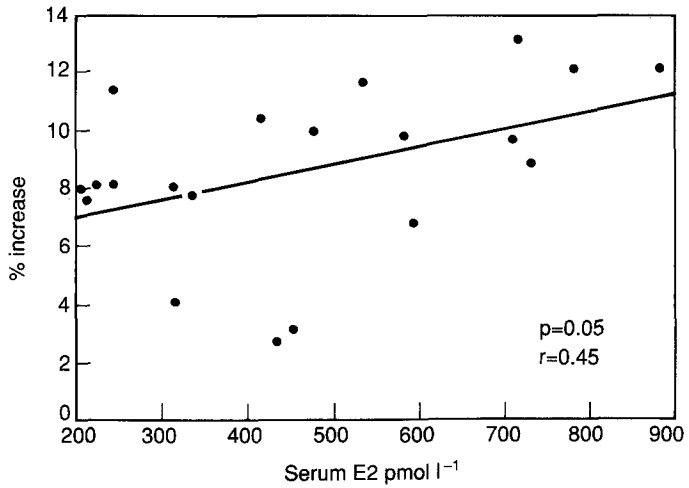

Figure 10. Relationship between serum oestradiol concentration and percentage increase in vertebral bone density.

with the plasma oestradiol values achieved at 1 year (Figure 10). There were no significant correlations between the increase in bone density and either testosterone level, age, menopausal age or initial bone density, thus confirming that the increased efficacy of implant therapy can be attributed to the higher oestradiol concentrations achieved, and that the added testosterone does not produce any further improvement in bone density than an oestradiol implant alone (Garnett et al, 1992).

The precise mechanism of action of oestrogen upon bone remains unknown. There are data demonstrating that oestrogen implants increase the collagen content of skin by up to 30% (Brincat et al, 1987), and it is possible that oestrogens may in a similar manner increase the collagenous matrix of bone. This is an exciting possibility, currently being investigated by means of serial histomorphometric studies of bone biopsy specimens. If confirmed, it suggests that oestrogen therapy may be able to promote healing of bone in which trabecular disruption has already occurred. The higher oestradiol concentrations and greater effects on bone achieved with implants would be of particular use in this circumstance.

Depression

A role for ovarian hormones in the regulation of mood is suggested by the very existence of postnatal depression, premenstrual syndrome and climacteric depression, and by the generally increased incidence of depressive disorders in women as compared with men. Oestrogen has been demonstrated in studies from this department to be a most effective therapy for both postnatal depression (Henderson et al, 1991), and premenstrual syndrome (Magos et al, 1986a; Watson et al, 1989). Ditkoff et al (1991) demonstrated that oestrogen elevated mood in asymptomatic postmenopausal women, and Klaiber et al (1979) were able to demonstrate a dose–response effect between oestrogen and mood in depressed women. More recently, Montgomery et al

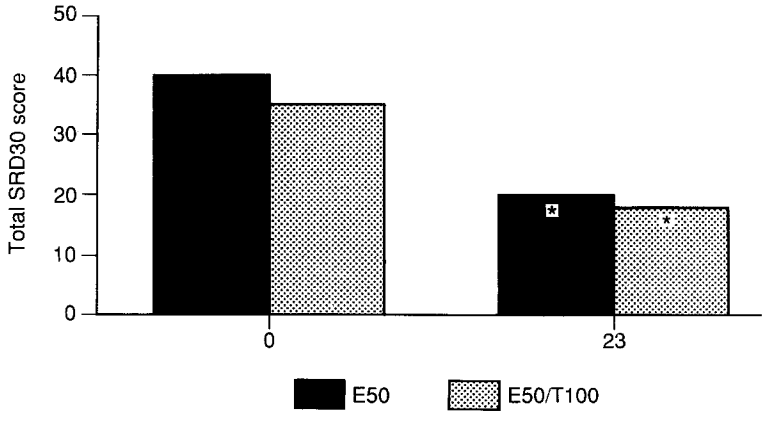

Figure 11. Perimenopausal depression and hormone implants: 23-month results, *, significant difference from baseline at $p < 0.05$. (Montgomery and Studd, unpublished data.)

(1987) demonstrated that oestradiol implants were significantly more effective than placebo in relieving depression and anxiety in climacteric women. The Self Rating Scale of Distress (SRD30) scores were significantly different from placebo by 2 months and a significant improvement compared with baseline was still evident at 23 months (Figure 11). These data support the hypothesis that oestrogen elevates mood in a dose-dependent manner. This is a relatively new concept, and further collaborative research needs to be done. It already seems clear, however, that oestrogen replacement is a better first choice treatment in many depressed climacteric women than psychoactive drugs, and that implants because of the higher oestradiol levels achieved are likely to be a more effective therapy for this indication than other routes of oestradiol administration.

LIPIDS AND COAGULATION

Ischaemic heart disease (IHD) and stroke are by far the two leading causes of death amongst postmenopausal women (OPCS, 1991). There is a wealth of data indicating that oestrogen replacement reduces the risk of IHD by approximately 40–50% (Stampfer and Colditz, 1991), and some data indicating a reduction in risk of stroke (Paganini-Hill et al, 1988), but almost all of these data concern the use of oral conjugated equine oestrogens. The beneficial effects of oral oestrogen have previously been considered to be largely due to their impact on lipids, raising HDL and reducing LDL (Bush et al, 1987). Oestradiol implants do raise HDL but result in a less consistent reduction in LDL (Lobo et al, 1980; Farish et al, 1984; Stanczyck et al, 1988).

There is growing awareness that lipids are not as important as previously believed, as evidence accumulates that oestrogen can affect arterial state in a number of different ways (see Chapters 4 and 5). For example, oestrogen has a direct atheroma-inhibiting effect upon arterial wall independent of cholesterol (Hough and Zilversmit, 1986), and oestrogens increase carotid and uterine artery blood-flow (Bourne et al, 1990; Gangar et al, 1991). This implies that the pharmacological effect on lipids seen with oral therapy is perhaps not so important. Further, because of the more physiological nature of implants and the higher blood concentrations of oestradiol achieved, beneficial effects may be greater than with oral therapy. The addition of testosterone implants, reduces slightly the rise in HDL seen with oestradiol implants alone, but has no effect upon the reduction in LDL (Farish et al, 1984).

Natural oestrogen given orally for postmenopausal hormone replacement has not been associated with any increase in risk of thromboembolism; indeed, as stated above, the incidence of stroke and heart attack is reduced. Despite the higher oestradiol concentrations achieved, implants appear to have no impact upon laboratory measures of clotting function, whereas oral therapy reduces anti-thrombin III (Thom et al, 1978). Because of the absence of a first-pass hepatic effect, risk of thromboembolism may thus be even lower with implants than with oral therapy.

COMPLICATIONS OF IMPLANT THERAPY

Apart from the local problems of bleeding, bruising and pellet extrusion there are few convincing complications of implant therapy. The long duration of effect of implants, which may be regarded as an advantage because it ensures compliance, may be a problem if discontinuation of therapy is desired, because the endometrial effect will be prolonged. Recently there has been some anxiety that continuous long-term therapy may result in supraphysiological levels of oestradiol. This has been incorrectly labelled as 'tachyphylaxis' (Gangar et al, 1989). The observation that such patients may also attend for repeat implants at progressively shorter intervals has led to the suggestion that women may become dependent upon oestrogens. In addition, there are problems associated with the mandatory use of progestogen in some women with a uterus.

Endometrial stimulation

Sturdee et al (1978) showed the high incidence of cystic hyperplasia in women receiving oestradiol implants and who omitted to take cyclical progestogen. They also showed that when progestogen was taken for 10 or 13 days each month the incidence was reduced to 0%. Paterson et al (1980) working in the same unit, subsequently showed that cyclical progestogen also reduced the incidence of adenomatous hyperplasia. If hyperplasia does occur with unopposed oestrogenic stimulation, then 3 months of treatment with progestogen (norethisterone 5 mg) for three weeks out of four will reverse 100% of cases of cystic hyperplasia and 50% of cases of adenomatous or atypical hyperplasia (Thom et al, 1979).

The need for a withdrawal bleed remains the single convincing complication of hormone replacement therapy and this is a potentially greater problem with implants because of their longer duration of action. Magos et al (1985) were able to achieve amenorrhoea in 60% of women taking continuous combined oral oestrogen and low-dose progestogen, but when continuous norethisterone was used in conjunction with 50 mg oestradiol implants, there was unacceptable irregular bleeding.

Thom et al (1981) showed that the oestradiol level 8 months after insertion of a 50 mg implant was still 160 pmol l^{-1}, and 12 months after insertion of a 100 mg implant was 202 pmol l^{-1}—three to four times the normal postmenopausal level. These data thus confirm the long-lasting effects of oestradiol implants, initially suggested by Hunter et al (1973) who reported low FSH concentrations persisting up to 26 months after implantation. Subsequently, Gangar et al (1990) reported that the effect of oestradiol implants lasted for more than 6 months. There is clearly a potential problem, when symptoms return, of patients believing that the implant has worn out and discontinuing the cyclical progestogen. It is vital that patients are warned of the prolonged uterine stimulation and instructed to take progestogens for at least 2 years after the last implant or until the progestogen no longer produces a withdrawal bleed.

Supraphysiological oestradiol concentrations (tachyphylaxis)

It has long been our view that women come back for repeat implants because climacteric symptoms have returned, although their hormone levels are in the premenopausal range (Cardozo et al, 1984). In spite of this, these patients obtain symptomatic relief from a repeat implant rather than from placebo (Brincat et al, 1984) indicating that it is the change in oestradiol concentration which determines symptoms rather than the absolute concentration. The relevance of this observation to the aetiology and treatment of the cyclical symptoms of premenstrual syndrome, a condition in which hormone levels are also within the normal premenopausal range, is apparent. Savvas et al (1988) reported the high oestradiol concentrations associated with implant therapy in their study of bone density changes. Gangar et al (1989) reported 12 patients with supraphysiological plasma oestradiol concentrations who had been collected from a pool of unknown size over several years. Garnet et al (1990) found a 3% incidence of oestradiol levels in excess of 1750 pmol l^{-1} in 1388 women seen during 1988 (Figure 12). These authors believed that there was a psychiatric component in the pathology of many of these patients. Of the 23 women initially treated for menopausal symptoms, 11 had a history of psychiatric referral for depression and nine had undergone a surgical menopause. Nine of the 15 women with premenstrual syndrome also had a history of psychiatric referral for depression. These women had a repeat implant every 4 months because of return of symptoms, and because of their psychiatric history most had an initial implant of 100 mg with maintenance doses of 75 mg. Thus these women with depression and PMS are a selected group who are also usually given high doses of oestradiol because it is believed that these affective symptoms respond optimally to high plasma oestradiol concentrations.

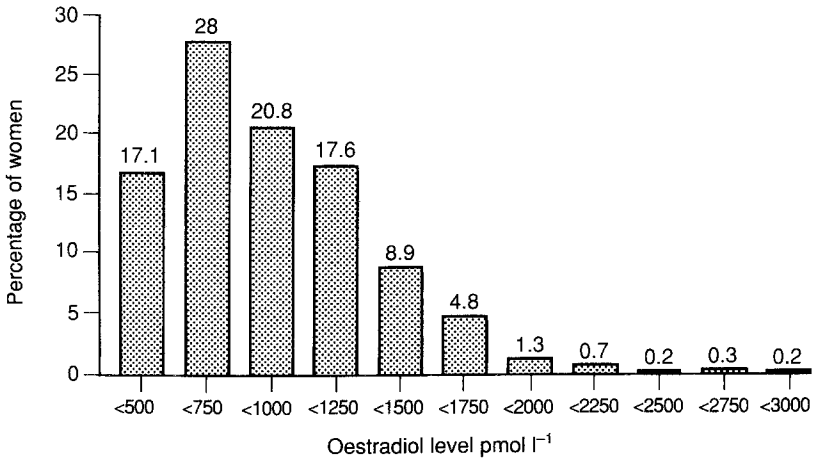

Figure 12. Oestradiol implants and tachyphylaxis. Concentrations in 1388 women. (Garnett et al, 1990.)

The only reported difference in outcome comparing normal and supraphysiological oestradiol concentrations is the greater incremental bone density found with higher levels (Savvas et al, 1988; Studd et al, 1990). It would seem that these moderately high oestradiol levels are no cause for concern and the suggestion by Gangar et al (1989) of a complete withdrawal of oestrogen therapy until oestradiol concentrations have dropped to 200 pmol l^{-1} is in our view wrong—and in severely depressed patients may be dangerous.

It should be stressed that the correct dose for climacteric symptoms is a 50 mg implant repeated every 6 months. It is irrational to use a higher dose at shorter intervals and then subsequently to believe that a complication of tachyphylaxis has been discovered.

Dependence on oestrogens

Bewley and Bewley (1992) considered that these patients may be exhibiting drug dependence with oestrogen replacement therapy. They accepted that oestrogens are psychoactive, having the ability to elevate mood in addition to other powerful psychological effects. Unfortunately their concept of oestrogen dependence was reported even in *The Times* (London) as suggesting that oestrogen may be as addictive as heroin. This is inappropriate and unfounded and was not the statement made by Bewley and Bewley. While accepting that the concept of dependence is important, it seems more likely that these women are simply dependent upon the new-found good health oestrogen replacement brings after years of insomnia, fatigue and depression. Supraphysiological concentrations of oestradiol are probably necessary for the relief of psychological symptoms in some women, and it is reassuring that there is no evidence that such levels are dangerous.

Cyclical progestogen

Cyclical progestogen therapy is necessary for the prevention of endometrial hyperplasia, in any woman with a uterus receiving oestrogen implants. We have shown that progestogen reproduces PMS symptoms and indeed the monthly addition of progestogen to an oestrogen-primed woman may be regarded as a model for the premenstrual syndrome (Magos et al, 1986; Studd and Magos, 1986b). This problem of progestogen intolerance is greater in patients with severe PMS who logically exhibit a central intolerance to their own cyclical endogenous progesterone. The long-term effect of oestradiol implants on PMS is good, but is limited by the need for cyclical progestogen. A full 13-day course may produce unacceptable PMS-type symptoms and the symptomatic improvement achieved from a shorter 7-day course may result in endometrial hyperplasia or, even if this is avoided, myometrial hypertrophy with an enlarged uterine cavity and menorrhagia. Of the 50 PMS patients on long-term implant therapy studied by Watson et al (1990) 20% subsequently had a hysterectomy—and were pleased to have such intervention, the mean uterine size of 133 g being significantly larger than normal. The same progestogenic problems occur,

albeit with reduced frequency, when treatment is given for indications other than PMS.

CONCLUSIONS

Oestradiol implants remain the most physiological method of administering oestrogen for a wide range of differing indications which include the climacteric syndrome, premenstrual syndrome, menstrual migraine, prophylaxis against and treatment of osteoporosis, and climacteric depression. The specific features of oestradiol implants are that they not only preserve the premenopausal oestradiol:oestrone ratio and avoid first-pass hepatic effects, but that they also achieve stable oestradiol levels in the upper end of the physiological range. Such hormone levels are important, as many oestrogenic effects, such as increasing bone density and elevating mood, demonstrate a dose–response effect. Thus, oestradiol implants achieve a greater increase in bone density over 1 year than any other mode of oestrogen administration, and they may be the only effective method of oestrogen administration for the treatment of certain psychological symptoms. Rather than being a problem, such high physiological levels are an advantage, with no evidence to the contrary. The addition of testosterone implants is an effective therapy for primary loss of libido and in some women decreased energy, and when used in combination with oestradiol implants has no adverse metabolic effects.

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