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Hormone Pellet Implantation for the Menopause and Premenstrual Syndrome

John Studd, M.D., F.R.C.O.G., and
Adam Magos, B.Sc., M.R.C.O.G.†*

Implants can be considered a pharmacologic delivery system designed to release a controlled amount of a drug into the systemic circulation over a long period. Several formulations have been developed, but the biodegradable fused crystalline pellet is the most widely available and the subject of this review.

Literature about hormone implants specifically is relatively scanty. Although this mode of therapy is popular in the United Kingdom, it is not so in the rest of Europe or the United States, where there are only 200 or so licensed users, its use being incomprehensibly limited by the FDA. Yet, hormone implantation offers definite advantages over the oral route of hormone replacement in terms of duration of action, convenience, metabolic effects, potency, and a more physiologic action, properties that deserve to be better exploited. Whether the newer percutaneous and vaginal preparations such as creams, patches, and rings, possessing similar properties but with the added advantage of ease of use, will supplant implants remains to be seen. At present, mainly thanks to a handful of enthusiasts, our knowledge of implants is increasing, and the method already has several proven indications in gynecologic practice.

HISTORICAL PERSPECTIVE

After earlier work in animals by Deanesly and Parkes in 1937,¹² the first record of an implant given for medical reasons appeared in the *British Medical Journal* in 1938. Bishop, an endocrinologist working at Guy's Hospital in London, described the case of a 20-

*Consultant Gynaecologist, King's College Hospital, London, England

†Senior Registrar in Obstetrics and Gynaecology, Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Maternity Department, Headington, Oxford, England

year-old woman who, having undergone bilateral oophorectomy for ovarian cysts, developed hot flushes 9 days after the operation.² She was successfully treated over a 2-year period with estrone, initially orally, subsequently by intramuscular injections, and finally by pure crystalline tablets implanted under the skin of the anterior abdominal wall. Using a dose of 14 mg of estrone, Bishop reported that vasomotor symptoms began to improve about 1 week after insertion of the tablet and were controlled for 4 to 5 weeks. He further commented that this mode of treatment compared favorably with the other routes of administration.

Eleven years later, Greenblatt and Suran published on the use of not only crystalline pellets of estradiol but also testosterone, progesterone, and desoxycorticosterone in the management of several endocrine and gynecologic disorders.²¹ They referred to conditions such as the climacteric syndrome and uterine hypoplasia (responding to estradiol), dysmenorrhea, endometriosis, fibroids, reduced libido, menopausal symptoms, and the prevention of estrogen-induced endometrial proliferation (responding to testosterone), "nervous tension," habitual abortion, and pubertal breast hypertrophy (responding to progesterone), and Addison's disease and panhypopituitarism (responding to desoxycorticosterone).

Several articles followed confirming the efficacy of estradiol implants for the treatment of symptoms associated with both a natural^{51,52} and, particularly, a surgical menopause.^{6,13,60} The other preparations never gained the same popularity, although Greenblatt, unarguably the premier champion of implant therapy, further advocated the use of testosterone implants for dysmenorrhea and psychosexual problems.²² In 1969, together with Empeaire, he extended the indications for estradiol implants by describing their anovulatory and thereby contraceptive properties.¹⁶

Despite the absence of major side effects and the repeated commendations of Greenblatt in the United States and Studd in the United Kingdom,⁶² however, the technique fell from general favor. Only a few isolated reports appeared in the medical press, once more describing the effects of estradiol implant supplementation in women who had bilateral oophorectomy.^{30,33}

More recently, after the demonstration by Sturdee and associates and others^{50,70} that endometrial hyperplasia and irregular uterine bleeding can be prevented by the concurrent administration of cyclic oral progestogens, renewed interest has been shown on both sides of the Atlantic as evidenced by extensive biochemical and symptomatic studies in pre- and postmenopausal women.

TYPES OF IMPLANTS

Long-acting implants are available in a number of formulations including steroid-containing permeable Silastic capsules and rods, fused crystalline pellets, and the newer polymer systems. The former

suffer from the inconvenience of not being biodegradable, thus necessitating their removal once all the hormone has been released. The latter have predominantly been developed to deliver progestogens for contraceptive purposes. Crystalline implants, being biodegradable and available as an estrogen from the earliest days, have always been the most popular method for gynecologic therapy.

Preparations include fused, white crystalline pellets of the three major sex steroids: 17β estradiol, testosterone, and progesterone (manufactured in the United Kingdom by Organon Laboratories), which are chemically identical to the respective endogenous hormones, and the progestogens norethindrone and levonorgestrel. The implants are small, cylindrically shaped, 3 to 6 mm in length and 2.2 to 4.5 mm in diameter depending on the dosage, made up of the hormone in a cholesterol base. They are individually packaged in presterilized glass vials.

17β ESTRADIOL

The major metabolic advantage of subcutaneous estradiol pellets over oral equivalents is the avoidance of the first pass liver effect and a physiologic action as represented by plasma estrogen levels comparable to the follicular phase of the ovarian cycle.⁶³ Implants are available in 25-, 50-, and 100-mg sizes. The typical menopausal replacement dose is 50 mg every 6 months⁶⁶; for anovulation, a step-down regimen starting at 100 mg and reducing to a maintenance dose of 25 mg every 6 months has been described by Greenblatt and co-workers. For the treatment of complaints linked to cyclic ovarian activity such as the premenstrual syndrome and menstrual migraine, the usual doses employed in our clinic range between 50 and 100 mg every 6 months.^{40,42}

TESTOSTERONE

Unlike the 17-alkylated oral methyltestosterone, which is hepatotoxic and icterogenic, the implant of the pure hormone is safe and is the route of choice for repeated administration. Doses include 50, 100, and 200 mg, 100 mg being the usual adjunct to estradiol replacement particularly when reduced libido and other psychosexual problems are present.⁶⁸ The original indication for the androgen, that of amelioration of menorrhagia, has been superseded by oral progestogens. Treatment is rarely complicated by significant virilization.

PROGESTERONE AND PROGESTOGENS

Both natural progesterone and the 19-norsteroid derivatives norethindrone and levonorgestrel are available as subdermal im-

plants. In addition to the gynecologic indications listed by Greenblatt and Suran,²¹ both the natural and synthetic hormones have been advocated for contraception.^{11,49} Pellets of the pure hormone, available at a dose of 100 mg, are now never used by us because they are often complicated by expulsion and result in irregular breakthrough bleeding when combined with estradiol. For this reason, these implants will not be considered further.

TECHNIQUE OF HORMONE IMPLANTATION

The procedure of hormone implantation has been described in detail by several authors including Greenblatt and Suran²¹ and Thom and Studd.⁷¹ It is an easy, quick, and safe office procedure carried out under local anesthesia. A no-touch technique is used with sterile instruments, but scrubbing up is not required.

Implants are usually inserted either into the subcutaneous fat of the abdominal wall 5 cm above and parallel to the inguinal ligament or into the fat of the buttocks. A small area of skin is cleansed with an antiseptic, and a track of underlying tissue is anesthetized with 1 per cent lidocaine solution, with or without added epinephrine. Once effective, a superficial 5-mm incision is generally made in the skin by using a pointed scalpel blade, but this step is optional. Trocars and cannulae, especially designed for implantation of hormone pellets (manufactured in the United Kingdom by Organon Laboratories), are available in two sizes depending on the diameter of the implant(s) to be inserted. The appropriate cannula, loaded with the sharp trocar, is pushed through the incision up to the hilt and into the subcutaneous fat. The rectus sheath, muscle, and any scar tissue should be avoided.

Once in position, the trocar is withdrawn, and the pellets are loaded into the barrel of the cannula by means of forceps. Care should be taken not to drop any of the implants—an easy accident considering their small size—because they cannot be resterilized. Precautions can be taken by first emptying the glass vials into a small gallipot and holding this under the cannula. Up to 12 pellets can be inserted, but the usual number is one or two. The blunt trocar (or obturator) is inserted fully into the cannula, thereby gently forcing the pellets into the subcutaneous tissues medial to the insertion site. The instrument is then withdrawn, and using dry dressing, pressure is applied over the wound for about 1 minute to prevent bleeding. When hemostasis is complete, the incision is covered with an adhesive bandage, and the patient is advised to keep the area dry for 24 hours. The whole procedure takes 2 to 3 minutes and is painless.

Complications are unusual. If insertion of the trocar is difficult, the skin incision should be enlarged with the scalpel. Prolonged bleeding after implantation usually responds to manual pressure, but

very rarely the skin has to be sutured as well. Bruising may follow such cases, but it is never extensive. A rare later complication is a wound infection, which usually responds to antibiotics, although the pellets may first be extruded. There is then no reason why an identical implant should not be inserted at a different site.

PHARMACOKINETICS OF IMPLANTS

ABSORPTION

The rate of absorption of sex steroid implants in humans has been described by Greenblatt and Hair.^{19,20} They showed that for compressed crystalline pellets for which the dose is proportional to size, absorption follows an exponential pattern, being fast early on and progressively slowing. Thus, for a 100-mg implant, the initial rate of absorption is 1 mg per day, falling to 0.5 mg per day by 3 months, and 0.35 mg per day by 6 months.¹⁹

The total rate of absorption appears to depend primarily on the surface area of the pellets, that is, on the number of pellets implanted rather than their size or weight. For instance, Greenblatt and Hair found that a 100-mg implant gave off only 50 per cent more material per day than a 50-mg implant, and that three 50-mg implants were the equivalent of two 100-mg pellets.¹⁹ Secondary factors they identified as affecting absorption included the density of the pellets, the size of the particles (crystals) that compose the pellet, and the site of implantation.

METABOLISM

Subcutaneous administration has important differences from the oral route. First, the gastrointestinal tract, where oral estradiol is preferentially converted to estrone, is bypassed.⁵⁵ Second, as intestinal absorption is rapid, oral therapy delivers a large bolus of the steroids into the portal circulation.³⁵ Third, the first pass effect on liver metabolism is avoided, whereby the orally administered hormones are largely metabolized and inactivated before reaching the systemic circulation.⁸ Implant action, therefore, is not affected to the same extent by drugs that induce liver enzymes.

Once absorbed, estradiol and testosterone implants are handled by the body as endogenous hormones and are largely inactivated in the liver. A tiny proportion of the androgen is also converted to estrogens, chiefly estril and estrone. It has been shown by Longcope and associates that the metabolic clearance rates of both sex steroids, a function of tissue blood flow and tissue extraction, do not change significantly with age.³⁴

EXCRETION

Both hormones are chiefly excreted in urine in the form of water-soluble glucuronides or sulfates of estradiol, estrone, and estriol (after estradiol) and androsterone and etiocholanolone (after testosterone).

METABOLIC EFFECTS

Relatively few publications have provided metabolic data about estradiol implants specifically, and even fewer have reported on testosterone. Considerably more information is available about percutaneous 17β estradiol, metabolically similar to the implant equivalent. These will be referred to when necessary.

SEX HORMONES

The acute and chronic effects of subcutaneous implants on plasma estrogens, testosterone, and gonadotropins have been determined by several investigators, mostly in postmenopausal women. Greenblatt and associates showed in three postmenopausal subjects that after an implant of a 25-mg estradiol pellet an increase in plasma estradiol concentrations can be detected by 6 hours, levels rising by a factor of three within 24 hours and a factor of four after 48 hours.²⁶ Plasma estrone levels remained unchanged during the study period. In contrast, the oral administration of micronized 17β estradiol was followed by a rise predominantly in plasma estrone levels. Lobo and colleagues studied 22 premenopausal women immediately after hysterectomy and bilateral salpingo-oophorectomy. They reported that plasma estradiol levels remained unchanged during the first 7 days of implantation, a discrepancy probably explained by the younger age of their study group.³³

The later effects of estradiol implants on previously untreated menopausal patients have also been studied in detail, with a broad consensus of results.^{7,30,33,72} The only study to report on a variety of dosage combinations, that of Thom and co-workers, showed that plasma estradiol and estrone concentrations came to a peak after 1 to 2 months of 50- or 100-mg pellets and began to decline thereafter.⁷² Both steroids remained within the normal reproductive range, but there was a differential effect with respect to the two major plasma estrogens: estradiol and estrone. The maximum increase in plasma estradiol level was five-fold after a 50-mg implant and 10-fold after 100 mg, whereas the figures for estrone were two- and four-fold, respectively (Table 1). Thus, independent of the dose of estradiol, the premenopausal ratio of the two estrogens (1 to 2:1) was re-created, an important relationship because it highlights the physiologic nature of hormone replacement with implants and contrasts with the effects of oral therapy.⁶¹

Table 1. *Effects of Different Routes of Natural Estrogen Administration on Pituitary and Ovarian Hormones*

	ROUTE OF ADMINISTRATION	
	<i>Subcutaneous/Percutaneous</i>	<i>Oral</i>
Estrone ⁶³	+	++
Estradiol ⁶³	++	+
Estradiol:estrone ratio ⁶³	++	--
LH ⁷²	--	-
FSH ⁷²	--	-
Prolactin ²⁸	nc	+

+ + / + : increased; -- / - : decreased; nc: no change.

The increase in plasma levels of estrogens was paralleled by opposite changes in the concentrations of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH).⁷² Levels fell to the premenopausal range within 2 weeks of implantation and to a minimum at 2 to 3 months (Table 1). Thereafter, the concentration of both gonadotropins slowly rose but remained in the premenopausal range even after 6 months, particularly after the higher dose of estradiol. These changes also contrast with the effects of oral replacement, which does not suppress gonadotropins into the premenopausal range.³²

As to the duration of action of estradiol implants, Thom and co-workers were able to detect an effect at 12 months, the duration of their follow-up.⁷² Hunter and colleagues, reporting on a study of almost 3 years, found that estrogen release was in fact maintained for up to 2 years after 100-mg estradiol implants.³⁰

The hormonal effects of repeated implant administration in the menopause have received less attention. Studying patients from the Dulwich Hospital Menopause Clinic, Cardozo and associates reported on the symptomatic and hormonal effects of regular, 6-month estradiol and testosterone implants.⁹ Their results suggested an accumulative effect with a progressive rise in estrone and estradiol concentrations and a fall in gonadotropin levels. Despite this pattern, the mean estrogen levels were within the premenopausal range after six successive implants even at the time of recurrence of symptoms. Simultaneously, Brincat and co-workers showed that the symptoms responded to active implants and not placebo in spite of the normal estradiol concentrations.⁴

Biochemical data on testosterone pellets in postmenopausal women have been presented by Thom and associates,⁷² Burger and colleagues,⁷ and Cardozo and co-workers,⁹ although only the first team looked at the hormone on its own as well as in combination with estradiol. Using a large dose of 200 mg of testosterone, Thom and associates found that the androgen alone had minimal effect on levels of gonadotropins or estrogens (or vasomotor symptoms) but did lead to a three-fold elevation of plasma testosterone concentrations by the second month of treatment. A similar but smaller increase was noted

when 100 mg of the androgen was given with 50 mg of estradiol, although with this regimen plasma levels of estrogens and gonadotropins were comparable with those seen when the estrogen was administered on its own. In contrast to the effects of estradiol pellets, the Cardozo study did not find the same degree of accumulation of testosterone on prolonged therapy, an observation probably explained by the shorter half-life of these implants.⁹

OVARIAN FUNCTION

As indicated earlier in this article, the application of estradiol implants has been extended to premenopausal women. Hormonal data from this group have been presented by Greenblatt and colleagues²⁵ and Asch and co-workers¹ in the United States and Magos and co-workers in the United Kingdom.^{40,41} The first publication reported on the immediate effects of 100 mg of estradiol and suggested that ovulation can be suppressed by this dose immediately, provided the pellet is inserted early in the cycle.²⁵ While this may be the case for the majority, we found that follicular development continued in almost half the cases studied during the first three cycles after the initial implant, with evidence of follicular rupture and luteinization in a small proportion up to that time (Figs. 1 and 2).⁴¹ No advantage was gained by using a higher dose of 150 mg of estradiol. Plasma estradiol levels during the first 6 months of treatment were comparable to those seen in postmenopausal women receiving the same treatment (Fig. 3) (unpublished observations). Once more, the potency of this

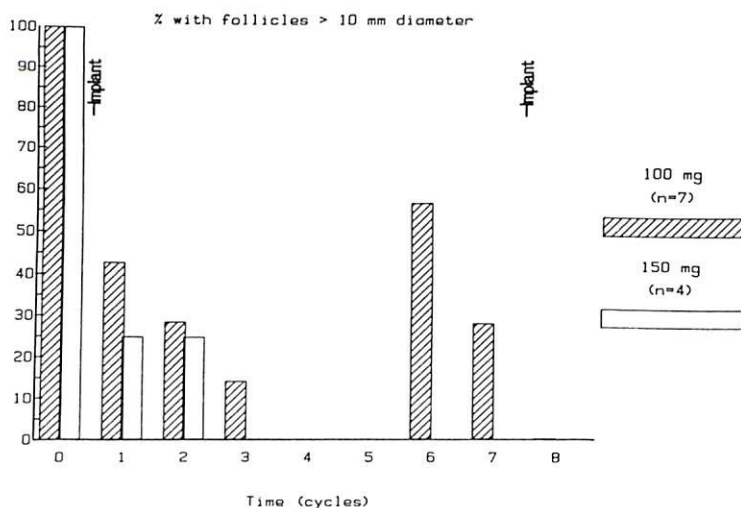


Figure 1. Follicular growth before and after treatment with estradiol implants.

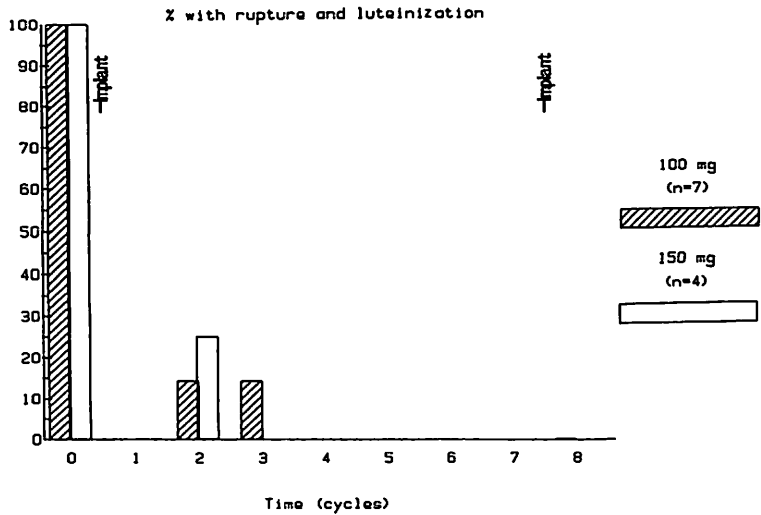


Figure 2. Follicular rupture and luteinization before and after treatment with estradiol implants.

route of therapy is supported by the observations of Greenblatt and colleagues, who showed in 1954 that up to 7.5 mg daily of oral equine estrogens are required to suppress ovarian function, a dose that is 6 to 12 times higher than the standard menopausal replacement dose.²²

The effects of regular therapy in this age group depend on dosage. With regular 6-month implants of 50 mg of estradiol, the

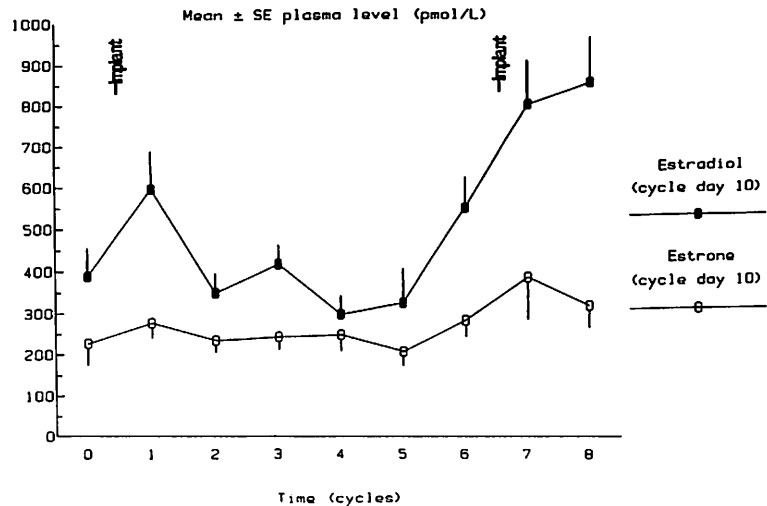


Figure 3. Mean plasma concentrations of estradiol and estrone in premenopausal women on day 10 of the menstrual cycle before and after treatment with 100-mg estradiol implants.

trend of gradual accumulation is the same as that found in postmenopausal women. In our study, 13 per cent of women who had been treated for longer than 3 to 4 years had supraphysiologic plasma levels of estradiol but not of estrone.⁴⁰ Pertinent to this finding, Greenblatt and co-workers had earlier shown that the dose of estradiol can be reduced every 6 months to a maintenance dose of 25 mg without any loss of contraceptive effect.²⁵ This regimen avoided any accumulation of plasma estradiol levels, although the same group of investigators subsequently reported that estrone levels did increase slightly.¹

SERUM BIOCHEMISTRY

Irrespective of the mode of administration, natural estrogens have no significant influence on general biochemical variables (Table 2). The effect on glucose tolerance is more controversial, but the only study reporting on estradiol implants noted no change.²⁵

HEPATIC METABOLISM

The important differences in the body's handling of exogenous estrogens are demonstrated by the differential effects of subcutaneous and oral routes of administration on the hepatic synthesis of proteins. It is evident from the results of subcutaneous or the metabolically similar percutaneous therapies that these routes are associated with minimal induction of protein synthesis in contrast to oral administration of natural estrogens (Table 3). In addition, unpublished work by Studd showed no change in liver enzymes or any pathology found by hepatic ultrasound studies. This has therapeutic implications; for instance, oral treatment should theoretically be

Table 2. *Effects of Different Routes of Natural Estrogen Administration on General Biochemical Variables*

	ROUTE OF ADMINISTRATION	
	Subcutaneous/Percutaneous	Oral
Glucose ⁵⁶	nc	nc
Glucose tolerance ²⁵	nc	nc
Urea ⁵⁶	nc	nc
Sodium ⁵⁶	nc	nc
Potassium ⁵⁶	nc	nc
Chloride ⁵⁶	nc	nc
Total protein ⁵⁶	nc	nc
Albumin ⁵⁶	nc	nc
Uric acid ⁵⁶	nc	nc

nc: no change.

Table 3. *Effects of Different Routes of Natural Estrogen Administration on Hepatic Metabolism*

	ROUTE OF ADMINISTRATION	
	<i>Subcutaneous/Percutaneous</i>	<i>Oral</i>
Liver enzymes (LDH, SGOT) ⁵⁶	nc	nc
Sex hormone-binding globulin (SHBG) ³³	+	++
Corticosteroid-binding globulin ³³	nc	
Pregnancy-zone protein (PZP) ²⁹	nc	++
Ceruloplasmin ²⁹	nc	++
Renin substrate ¹⁵	nc	++

+ +/+ : increased; --/- : decreased; nc: no change.

avoided in patients with high blood pressure as the increased production of renin substrate may aggravate the hypertension.

LIPID METABOLISM

This is an area of prolific research because of the link between lipids and cardiovascular disease. The consensus is that subcutaneous, percutaneous, and especially oral therapies produce favorable changes in the various lipid and lipoprotein fractions (Table 4). For instance, serum levels of high-density lipoprotein (HDL) cholesterol are increased, particularly the HDL₂ fraction as shown by studies in our clinic,¹⁰ and the ratio of HDL:LDL cholesterol is elevated. These effects have been interpreted as being protective against ischemic heart disease,⁴⁷ a view supported by some of the epidemiologic data concerning estrogen as summarized by Henderson and colleagues.²⁷ More recently, however, the relevance of HDL to coronary artery disease has been challenged, at least for men.⁵³

Table 4. *Effects of Different Routes of Natural Estrogen Administration on Lipid Metabolism*

	ROUTE OF ADMINISTRATION	
	<i>Subcutaneous/Percutaneous</i>	<i>Oral</i>
Cholesterol ⁵⁶	nc	+
Triglycerides ⁵⁶	nc	+
Phospholipids ⁵⁶	++	++
Low-density lipoprotein (LDL) ⁵⁶	--	--
Very low-density lipoprotein (VLDL) ⁵	--	nc
High-density lipoprotein (HDL) ⁵⁶	+	++
HDL subfraction 1 ⁵	-	
HDL subfraction 2 ⁵	+	++
HDL subfraction 3 ⁵	+	+

+ +/+ : increased; --/- : decreased; nc: no change.

BONE METABOLISM

Estrogen inhibits bone resorption and improves calcium balance, changes that have been proposed as the explanation for the prevention of postmenopausal osteoporosis by replacement therapy (Table 5). There seems to be little difference between the various routes of administration, and it has recently been shown by Ralston and colleagues that testosterone pellets, although anabolic, do not augment the benefits secondary to estradiol implants.⁵⁴

An alternative line of research by Brincat has shown that postmenopausal women receiving estradiol and testosterone implants had significantly greater skin collagen content and thickness compared with untreated controls.³ This observation suggests that increased bone resorption may not be as important in postmenopausal bone as decreased collagen formation by osteoblasts. Brincat has also shown that postmenopausal women with thin skin and reduced skin collagen will replace virtually all the skin collagen after 9 months of therapy with 50-mg pellets of estradiol.³

HEMOSTASIS

Adverse changes in the clotting and fibrinolytic systems are well-known effects of synthetic estrogens such as ethinyl estradiol. Data about orally administered natural estrogens are somewhat contradictory, but our studies comparing this route with subcutaneous estradiol implants did not report any significant alterations in hemostatic variables (Table 6).^{69,73} Although confirmation is awaited, Elkik and colleagues found that oral conjugated equine estrogens reduced the plasma concentrations of antithrombin III, a natural coagulation inhibitor, unlike percutaneous 17 β estradiol.¹⁵ If this proves to be a genuine effect, modes of therapy with minimal effects on hepatic protein synthesis would appear preferable.

Table 5. *Effects of Different Routes of Natural Estrogen Administration on Bone Metabolism*

	ROUTE OF ADMINISTRATION	
	Subcutaneous/Percutaneous	Oral
Calcium ⁵⁴	--	--
Phosphate ⁵⁴	--	--
Alkaline phosphatase ⁵⁴	nc	nc
Renal calcium excretion ⁵⁴	--	--
Renal phosphate threshold ⁵⁴	--	--
Parathyroid hormone ⁷⁵	+ +	+
Calcitonin ⁷⁵	+	+
25 dihydroxyvitamin D/1,25 dihydroxyvitamin D ⁷⁵	-	-
Collagen (in skin) ³	+ +	

+ +/+ : increased; --/- : decreased; nc: no change.

Table 6. *Effects of Different Routes of Natural Estrogen Administration on Hematologic Variables*

	ROUTE OF ADMINISTRATION	
	<i>Subcutaneous/Percutaneous</i>	<i>Oral</i>
Platelet count ⁶⁹	nc	nc
Platelet aggregation ⁶⁹	nc	nc
Plasminogen activation ⁶⁹	nc	nc
Fibrin degradation products ⁶⁹	nc	nc
Kaolin-cephalin clotting time ⁶⁹	nc	nc
Antithrombin III ¹⁵	nc	--

--/- : decreased; nc: no change.

ENDOMETRIAL EFFECTS

Estrogens cause endometrial proliferation, and estradiol implants are no exception. Indeed, because pellets are associated predominantly with an increase in the circulating concentration of estradiol, shown to be the major intracellular estrogen,³¹ they are all the more potent. Despite this and the link between prolonged unopposed estrogen therapy and endometrial carcinoma,⁶⁵ treatment with estradiol implants has been shown to be safe in both pre- and postmenopausal women, provided it is combined with cyclic oral progestogen.^{25,40,50,67,70} Sturdee and colleagues showed that just as with oral replacement therapy the degree of endometrial protection afforded by progestogens was duration rather than dose dependent. The risk of hyperplasia was negligible, if the tablets are taken for 10 or more days each calendar month (Table 7).⁷⁰ Simultaneously in the United States, Gambrell reported that women receiving estrogen/progestogen hormone replacement therapy are at a reduced risk of developing endometrial carcinoma compared with untreated controls.¹⁷

We have demonstrated that progestogens are often associated with minor symptomatic side effects similar to the premenstrual syndrome.⁴³ Noncompliance is thus always a potential problem with

Table 7. *Endometrial Histology after Natural Estrogens and Cyclic Oral Progestogens*

DURATION OF PROGESTOGEN (DAYS/MONTH)	ABNORMAL HISTOLOGY (%) ROUTE OF ADMINISTRATION	
	<i>Subcutaneous</i>	<i>Oral</i>
0	56	15
5	8	—
7	12	3
10	3	2
>10	0	0

combined hormone therapy. As is apparent from Table 7, it is especially important with implants that the monthly course of progestogen be taken. Unless the progestogen is reliably taken for more than 10 days per calendar month, regular outpatient endometrial biopsies are indicated, and any endometrial hyperplasia should be treated with an extended course of progestogen for two to three cycles.⁶⁷

As previously discussed, progestogens are traditionally given cyclically. We have investigated continuous low-dose progestogen therapy in combination with estradiol and testosterone implants in an attempt to avoid the necessity of monthly withdrawal periods.⁴⁴ Starting with doses of norethindrone ranging from 0.35 to 5 mg daily, it was found that unacceptable breakthrough bleeding affected the majority of women, and only eight of the 71 women (11 per cent) in the study group achieved long-term amenorrhea of over 12 months. This was in direct contrast to our experience with oral continuous combined therapy, where irregular bleeding early on tended to be slight and eventual amenorrhea was the norm.⁴⁵

Although testosterone has been used to treat menorrhagia,²² it does not prevent the endometrial stimulation caused by concurrent therapy with estrogens. Whether the androgen augments the antiproliferative actions of progestogens to any significant degree remains to be determined.

BREAST DISEASE

Apart from the putative thrombotic, cardiovascular, and endometrial risks of hormone replacement therapy, now more apparent than real, the other major concern has been over a possible link with breast cancer, the most common malignancy in women. It is not the purpose of this article to review the available evidence, particularly as there are no data about estradiol or testosterone implants, except for the palliative use of testosterone pellets in advanced carcinoma.²¹ Suffice it to say that a recent review of the literature by Gambrell concluded there is no evidence that estrogens truly increase the risk of breast cancer, while the addition of progestogen seems to reduce the incidence.¹⁸

IMPLANTS AND THE MENOPAUSE

Undoubtedly, the major indication for estradiol implants at present is for the management of the menopausal complications, be it for the symptomatic relief of vasomotor instability, vaginal atrophy, or other climacteric complaints or for prophylaxis against osteoporosis. Most commonly, as originally described by Bishop in 1938,² pellets are given to premenopausal women who have undergone hysterectomy and bilateral oophorectomy for nonmalignant indications, when

it represents a convenient method of hormone replacement. The effectiveness of estrogen pellets under these circumstances has been repeatedly confirmed.^{6,13,30,33,60,66}

Implants are less often given to women with intact uteri, oral therapy generally being chosen, although the efficacy of implants has been well documented.⁹ This preference stems from the fear of uncontrolled uterine bleeding with estradiol pellets, an irrational worry if treatment is combined with cyclic oral progestogens.⁶⁶ It should also be apparent from the preceding discussion that subcutaneous therapy offers definite metabolic advantages over the oral route. A direct symptomatic comparison of the two modes of treatment is, however, still awaited.

Although there can be little doubt that estradiol pellets are an effective therapy for the climacteric, implants have only now been subjected to a placebo-controlled study. Montgomery and colleagues concentrated on the psychologic rather than somatic effects of such treatment in 70 peri- and postmenopausal women. They reported significant benefits of active treatment over placebo.⁴⁸ Earlier work also from our clinic showed that a combination of estradiol and testosterone pellets was significantly superior to placebo for almost all physical as well as psychologic symptoms.⁴

The latter study raises a controversy, namely the role of testosterone supplementation in menopausal therapy. Androgens have been advocated for the treatment of reduced libido for many years by Greenblatt, a common problem at the menopause.²³ Although estrogens themselves have been shown to improve sexual functioning,⁴⁶ possibly because of relief of vaginal dryness and dyspareunia, data generated without a control group presented by Studd and co-workers and Burger and colleagues showed that a combination of the two sex hormones results in a superior response.^{7,68} These impressions have been challenged by one controlled study¹⁴ but confirmed by another.⁵⁹ Once more, differences in patient groups may explain the apparent discrepancy. While Dow and co-workers monitored women who had undergone a natural menopause,¹⁴ the later study included only women who had bilateral oophorectomy. Vermeulen has shown that the postmenopausal ovary is an important source of androgens, secreting 50 per cent of plasma testosterone and 30 per cent of androstenedione.⁷⁴ While a direct relationship between testosterone levels and libido has never been shown, it may be that oophorectomized "hypoandrogenic" women would gain more benefit from such therapy. Certainly, Sherwin and Gelfand have demonstrated, once more in women after oophorectomy, that combined oral estrogen/testosterone treatment is statistically superior to estrogen alone with respect to energy, well-being, and appetite.⁵⁸ The same investigators had already made the observation that the androgen on its own failed to alleviate vasomotor symptoms despite elevated plasma estrogen levels.⁵⁷ It is therefore possible that some type of synergy occurs with combined therapy, perhaps mediated by alterations in the metabolism of sex hormone-binding globulin.

Whatever the ultimate truth concerning testosterone supplementation, in the absence of other percutaneous preparations, there can be little argument that the optimum route of administration of this hormone is not oral but by subcutaneous implant.

IMPLANTS AND THE PREMENOPAUSE

The finding by Empeaire and Greenblatt in 1969 that estradiol pellets can suppress ovulation in premenopausal women opened the door to a totally new set of applications.¹⁶ This and the later updates by the same investigators describing a step-down regimen of 6-month implants combined with cyclic oral progestogen showed the contraceptive efficacy of this approach.^{1,24,25} During their entire series of over 7000 cycles, there were only five pregnancies, four within the first 6 months of the first 100-mg implant and one with the maintenance dose of 25 mg. As rightly pointed out by the authors, this method of birth control has several advantages over conventional techniques for the middle-aged woman.

The potential of such anovulatory therapy for the management of cyclic disorders such as the premenstrual syndrome was realized by Studd.⁶⁴ From the mass of essentially negative data about this nebulous condition, it was apparent that cyclic ovarian activity was of primary importance in pathogenesis.³⁶ This is not unexpected when one realizes that well over 200 physical, psychologic, and behavioral changes normally accompany ovulation.³⁷ In the absence of a specific biochemical abnormality in women suffering from the premenstrual syndrome, it seemed that the syndrome represented an exaggerated response to these many bodily fluctuations.

The corollary of considering cyclic ovarian activity as fundamental in the etiology of the premenstrual syndrome is that suppression of ovulation should abolish symptoms.⁶⁴ This hypothesis was initially tested by us in a pilot uncontrolled study of 92 women, treated for up to 7 years with regular anovulatory doses of estradiol pellets and cyclic oral progestogen. Testosterone implants were also employed in 87 per cent of cases, for those who complained of a severe loss of libido in addition to their premenstrual problems.

Retrospective analysis showed that implant treatment was associated with complete or almost complete relief of premenstrual syndrome in 84 per cent of cases, with only three women failing to respond.⁴⁰ The treatment, this time without the androgen, was subsequently tested under placebo-controlled conditions of 68 women over a 10-month period. The results of this prospective study confirmed the efficacy of estradiol implants, even in the face of an initial response to placebo pellets of 94 per cent.³⁹ Trend analysis was used to assess the daily symptom records.³⁸ Active treatment proved to be superior to placebo for all six adverse symptom clusters of a modified Moos Menstrual Distress Questionnaire after the first 2 months, a differential response that was maintained for the duration of the follow-up (Fig. 4). Compared with other anovulatory measures, such

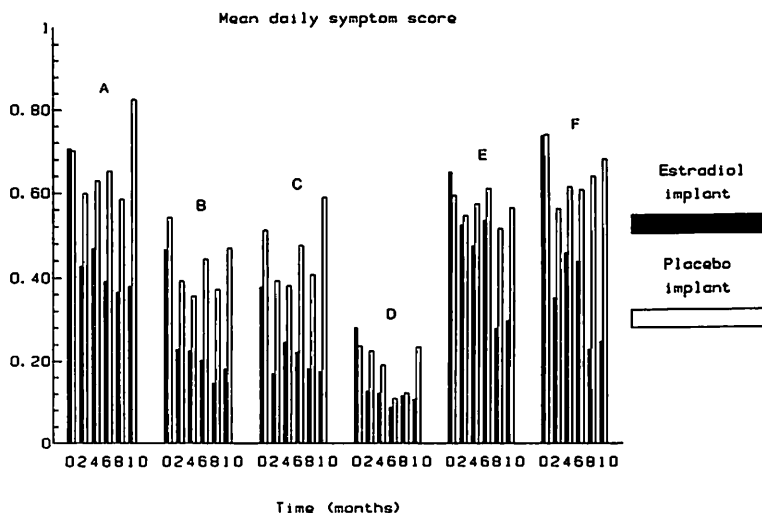


Figure 4. Effect of 100-mg estradiol implants on mean daily symptom scores in the premenstrual syndrome.

treatment is not only effective but also safe for the age group typically affected by this disorder (unlike the combined contraceptive pill), well tolerated (unlike danazol), and suitable for long-term therapy (unlike LH-RH agonists).

The premenstrual syndrome is by no means the only condition with a close link with cyclic ovarian activity. A recent review of the literature revealed that over 70 other medical disorders are precipitated or aggravated by ovulation.³⁷ One, menstrual migraine, has already been shown by us to respond to estradiol pellets.⁴² Many more, including common ailments such as diabetes, rheumatoid arthritis, asthma, and epilepsy await investigation along these lines. Our understanding of the therapeutic indications for implants, particularly estradiol, is clearly still in its infancy.

SUMMARY

Sex hormone implants have been available for almost 50 years, but only a few clinicians administer them regularly. Implants represent a physiologic mode of therapy with many metabolic advantages over other routes. Surprisingly, they are relatively ignored by physicians. This may well reflect their surgical nature, although the technique of hormone implantation is simple and fast and obviates daily oral medication. As the list of indications for hormone pellets grows, more patients will take advantage of the benefits they offer.

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120 Harley Street
London W1N 1AG
England