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ALTERNATIVES TO ORAL ESTROGEN REPLACEMENT

Transdermal Patches, Percutaneous Gels, Vaginal Creams and Rings, Implants, and Other Methods of Delivery

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In this article, the pharmacokinetics of oral and parenteral estrogens are compared. Each parenteral form of estrogen replacement is reviewed, including available data regarding effects on the cardiovascular and skeletal systems. Although emphasis is given to forms of parenteral estrogen currently available in the United States, information is also provided regarding alternatives available to women in other countries.

ORAL AND PARENTERAL ABSORPTION OF STEROIDS

Oral Estrogen. Estrogen taken orally is absorbed through the intestinal wall where a fraction is converted to estrone or estradiol glucuronide.[63, 90] Estrogen then travels to the portal circulation, reaching the liver in high concentrations. In contrast, during the reproductive years, endogenous estrogen made by the ovaries or in adipose tissue is secreted into the circulation and brought to target organs before reaching the liver. Therefore, the concentration of estrogen in the liver is much higher with oral ingestion than with endogenous production, resulting in the *first-pass effect* on hepatic protein synthesis. In addition, the relative effect of high levels of estrogen in the liver is greater than it would be in other tissues because the liver extracts estrogen to a greater extent than the uterus or brain.[105]

Oral estrogen therapy stimulates the synthesis of hepatic proteins, including

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binding globulins, clotting factors, renin substrate, and lipoproteins.[45, 107] At doses that produce similar depression of gonadotropins, the hepatic effects of oral estrogen are greater than parenteral estrogen; this is likely due to the first-pass effect and also possibly due to high levels of estrone that may be active in the liver. Hepatic effects depend on the type of estrogen ingested as well as the route of administration. For example, equine and synthetic estrogens, on a per weight basis, stimulate the synthesis of binding globulins and renin substrate more than do other estrogens.[70] Because these effects of oral estrogen are produced by supraphysiologic concentrations of estrogen in the liver, the hepatic effects of any oral estrogen can be considered pharmacologic rather than physiologic.

After initial metabolism in the liver, estrogen enters the systemic circulation in a much lower concentration than in the enterohepatic circulation. With the doses and forms of oral estrogen used clinically, serum levels of estradiol are similar to those of the early follicular phase in cycling women (Fig. 1), but owing to metabolism by the intestinal wall and the liver, oral estrogens produce higher circulating estrone concentrations than seen in the reproductive years or in women on parenteral estrogen therapy. High levels of estrone are produced by nearly all oral estrogens, including natural estrogens (estradiol and estradiol

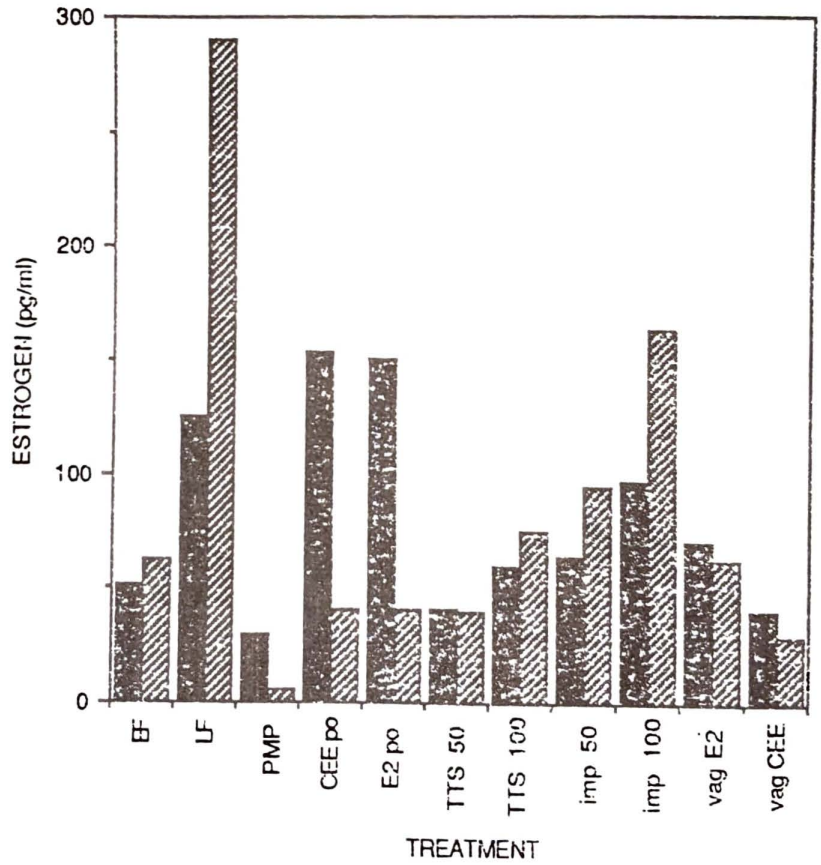

Figure 1. Circulating estrogen levels with oral and parenteral administration. Levels were measured as follows: approximately 12 hours after oral or vaginal dose, mean during 72 hours for TTS, average over several months for implant. Solid bar = estrone, striped bar = estradiol. EF = early follicular phase, LF = late follicular phase, PMP = postmenopausal, CEE po = CEE 0.625 mg po, E2 po = E2 1 mg po, imp 50 = implant 50 mg, imp 100 = implant 100 mg, vag E2 = vaginal estradiol 0.2 mg, vag CEE = vaginal CEE 1.25 mg. (*Data from* references 60, 62, 66, 85, 88, 94, 104, 114.)

valerate), conjugated equine estrogens (CEE), and synthetic estrogens. The ratio of estrone to estradiol is much higher with oral estrogen replacement than before the menopause when this ratio is approximately 1:1. Although no negative clinical consequences of these high estrone concentrations have yet been demonstrated, studies have not been done to specifically examine the impact of supraphysiologic estrone levels on outcomes such as breast cancer.

With CEE (Premarin), even these high serum levels of estrone do not reflect the total amount of circulating estrogen. This is because CEE consist of three major components: estrone sulfate (50% to 60% of the preparation) and two estrogens not normally made by humans, equilin sulfate (20% to 30%) and dihydroequilin sulfate (15%). The levels of equilin estrogens produced by oral doses of 0.625 or 1.25 mg of CEE are many times higher than the levels of estradiol or estrone achieved and are only measured by assays that are not readily available.[112]

Parenteral Estrogen. Estrogen is well absorbed through the skin and subcutaneous fat, the vagina, the nasal mucosa, and sublingually. The absorption of all of these forms of parenteral therapy share one important feature: the first-pass effect through the liver is avoided. The concentration of estrogen reaching the liver is physiologic. Consequently, the changes in binding globulins and lipoproteins are less dramatic than with oral therapy and there are no elevations of triglycerides or clotting factors. Some effect of parenterally administered steroids on lipoproteins is demonstrable, however, perhaps because steroids reach the liver soon after entering the circulation as blood circulates through the liver at approximately 1 L/min. Furthermore, when given in doses that produce comparable circulating estradiol levels and suppression of gonadotropins, parenteral conjugated equine estrogens produce greater hepatic effects than parenteral estradiol.

With parenteral therapy, the estrogen does not undergo the metabolism to estrone in the intestinal wall. Consequently, the estrone to estradiol ratio with parenteral therapy is lower and more physiologic than with oral administration.

Potency of Oral and Parenteral Therapy. The effect of an estrogen depends on the type of estrogen, the dose, and the route of administration. The potency of a given therapy will also vary depending on which target tissue and effect is considered. In this review of alternatives to oral estrogen, the target tissues and effects that are addressed include the effect of estrogens on gonadotropins, synthesis of liver proteins (e.g., sex hormone–binding globulin and renin substrate), serum lipid and lipoprotein levels, bone density and metabolism, vasomotor symptoms, vaginal cytology, and endometrial proliferation.

TRANSDERMAL ESTROGEN REPLACEMENT

Estradiol Transdermal Therapeutic System

Description

The estradiol transdermal therapeutic system (TTS) (Estraderm), or "patch" as it is often called, releases 17β-estradiol continuously through a rate-limiting membrane applied to the skin. The type of patch in current clinical use and the most extensively tested is a reservoir system. The four layers comprising this patch from its visible surface to the patient's skin are as follows: (1) an occlusive backing that prevents evaporation; (2) a drug reservoir of estradiol dissolved in

alcohol, which carries estradiol to the skin; (3) a membrane that controls the release of estradiol; and (4) an adhesive that attaches the patch to the skin. These patches have a surface area of 10 cm^2 (for a patch that delivers 50 μg of estradiol per day, the TTS 50) to 20 cm^2 (for a patch that delivers 100 μg of estradiol per day, the TTS 100). Estradiol-TTS may be applied to the buttocks or abdomen on a clean, dry area but should not be applied to the breasts.

Less than 10% of the drug contained in the estradiol-TTS is delivered[35] because at the end of approximately 4 days, most of the alcohol, which carries the estradiol to the skin, has been delivered. After this time, the only force driving estradiol to the skin is the concentration gradient, so the rate of absorption decreases and becomes erratic. The patch must, therefore, be applied twice weekly.

A new TTS (Systen) is a matrix system, which has been designed in an attempt to reduce the likelihood of skin irritation and problems with patch adherence that occur with the reservoir system.[18, 115] This system releases 50 μg of estradiol per day and has a surface area of 16 cm^2, slightly larger than the TTS 50 in use in the United States. It has a thin monolayered adhesive film containing estradiol located under a transparent occlusive foil backing. Because the estradiol and the adhesive are incorporated in a single layer, a fluid reservoir is not needed.[27] This patch is applied twice each week.

Pharmacokinetics

Estrogen. The serum estradiol levels achieved with the TTS depend on the dose. Patches are available in the United States that deliver either 50 μg (0.05 mg) or 100 μg (0.10 mg) per day, and other patches have been tested clinically that deliver 25 μg or 200 μg per day. These values compare with 60 to 600 μg per day produced by the ovary during the reproductive years and less than 20 μg/day after menopause.[112] Patches that deliver daily doses of 25, 50, and 100 μg result in serum estradiol levels of approximately 20 to 25, 35 to 50, and 80 to 110 pg/mL respectively.* The levels with the two higher-dose patches are similar to those of a cycling woman in the follicular phase. The patches used currently appear to deliver more estradiol and produce circulating estradiol levels that are approximately 30% higher than the older, prototype systems.[15, 81]

Transdermal therapy produces a physiologic ratio of estrone to estradiol of approximately 1:1. Serum estrone levels for the 25, 50, and 100 μg patches are approximately 30, 40 to 45, and 60 to 70 pg/mL respectively.[81, 85, 94] With oral therapy, estrone levels are much higher (see Fig. 1). After a patch is applied, estrogen levels rise gradually without an initial bolus to a high level as seen with oral therapy, and reach a steady-state level at approximately 2 hours.[48] Patches produce more constant serum estrogen levels over a given 24-hour period than achieved with oral estradiol (Figs. 2 and 3). With oral ingestion, serum levels of estradiol and estrone vary greatly over the course of a day,[94] peaking at high levels and gradually falling to a nadir just before administration of the next dose. Although the patch produces less variance in serum estradiol levels than oral estrogen, estrogen levels will gradually decline during the 3 to 4 days that a patch is worn, and an absolute steady state is not achieved.[48, 94, 104] For example, Scott et al[94] reported that the estradiol-TTS 50 produced serum estradiol levels that varied from a mean of 50 pg/mL on day 1 to 28 pg/mL 3 days after application of the system, a nearly 50% decrease.

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*References 56, 81, 85, 94, 95, 96, 104.

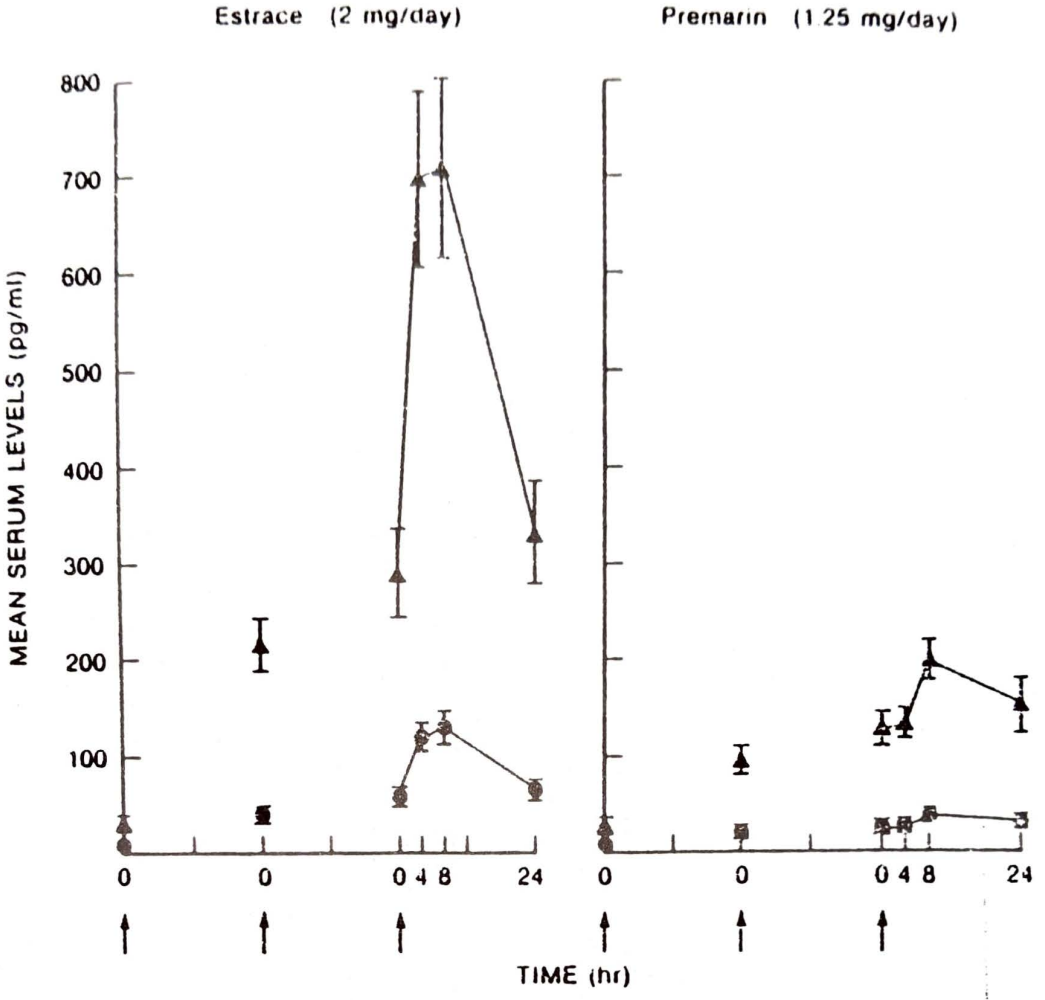

Figure 2. Mean serum levels of estradiol and estrone with the use of Estrace (2 mg/day) and Premarin (1.25 mg/day). ● = estradiol, ▲ = estrone, I = SE, ↑ = dose given (orally in the morning). (*From* Powers MS, Schenkel L, Darley PE, et al: Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17β-estradiol: Comparison with conventional oral estrogens used for hormone replacement. Am J Obstet Gynecol 152:1099, 1985; with permission.)

Because estradiol has a short half-life of less than 1 hour, blood levels decline rapidly after an estradiol patch is removed.[48] Urinary output of estradiol conjugates increases to 3 to 5 times baseline and returns to baseline within 2 to 3 days after the patch is removed,[85] indicating little or no accumulation of estrogen in the body. This can be compared with oral therapy in which urinary output of estradiol conjugates increases to about 100 times the baseline and does not approach baseline until 7 to 8 days after the last dose.

Jensen et al[52] determined that smokers on hormone replacement therapy have lower levels of serum estrone and estradiol than nonsmokers, most likely because of increased hepatic metabolism of estrogens in the smokers. Theoretically, a nonoral route of estrogen administration could provide higher circulating estrogen levels by eliminating the first-pass effect. However, other investigators[13] have demonstrated that the small increase in clearance of estrogen is not significant enough to warrant increasing the dose of oral estrogen. By extrapolation,

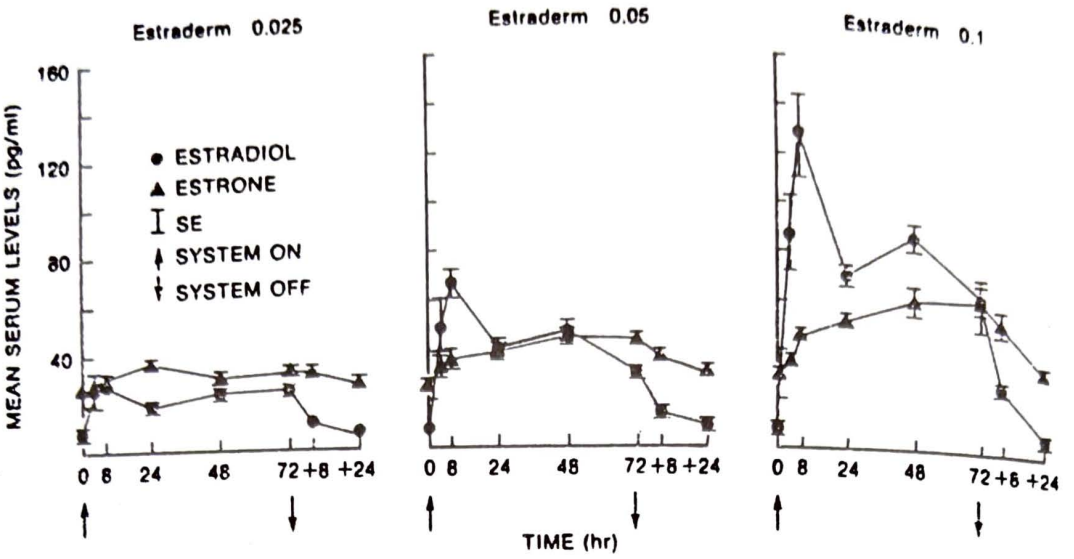

Figure 3. Mean serum levels of estradiol and estrone with use of Estraderm 0.025, 0.05, and 0.1 mg/day. ● = estradiol, ▲ = estrone, I = SE, ↑ = system on, ↓ = system off. (*From* Powers MS, Schenkel L, Darley PE, et al: Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17β-estradiol: Comparison with conventional oral estrogens used for hormone replacement. Am J Obstet Gynecol 152:1099, 1985; with permission.)

smoking and concern for low estrogen levels is probably not an indication for nonoral estrogen replacement.

Progestin. For women with a uterus, most gynecologists advise administration of a progestin to reduce the risk of endometrial carcinoma resulting from estrogen therapy alone. Currently, the progestin must be given orally, requiring the patient who is being administered estradiol-TTS to use a pill and a patch. Because some patients find it bothersome to take two forms of medication, adherence with the recommended progestin may be a problem.

To address this problem, transdermal progestin therapy has recently been brought to clinical testing.[56, 119] Because of its lower potency, natural progesterone necessitates an unacceptably large patch size. In contrast, norethindrone is a very potent progestin and therefore only small doses are needed. A combined estradiol and norethindrone patch (Estragest) has a surface area of 10 cm^2, the same as the conventional estradiol patch. Transdermal norethindrone acetate produces little change in carbohydrate metabolism, in contrast to some of the oral progestins, which produce unfavorable changes in carbohydrate metabolism. Norethindrone, a C-19 nortestosterone derivative, however, produces a greater reversal of estrogen-induced lipid changes than C-21 derivatives such as medroxyprogesterone acetate.

Effects of Estradiol-TTS

Gonadotropins and Binding Globulins. Although suppression of gonadotropins is of no clinical significance, the effect of estrogens on gonadotropins serves as a marker of estrogen potency. With patches delivering daily doses of 50 to 100 μg, follicle-stimulating hormone (FSH) levels fall by 17% to 40%.[15, 96] Decreases in FSH and luteinizing hormone (LH) seen with 50 and 100 μg patches are similar to those seen with 0.625 and 1.25 mg of oral CEE, respectively.[15] The

decrease in FSH produced by the 50 μg patch is also similar to that of a 2-mg dose of oral estradiol.[85] As with oral estrogen, however, even high doses do not restore FSH or LH to premenopausal levels. Possible reasons for this include lack of inhibin production and lower average estrogen levels than produced by the ovary during the reproductive years.

Baseline levels of cortisol-binding globulin (CBG), sex hormone–binding globulin (SHBG), and thyroid-binding globulin (TBG) in postmenopausal women not on hormone replacement are similar to those in premenopausal women. Oral CEE stimulate synthesis of CBG, SHBG, and TBG.[45] There have been no detectable health consequences attributable to high levels of these hepatic proteins, and they instead serve as markers of the hepatic response to estrogen. With transdermal therapy, elevations of renin substrate, CBG, SHBG, and TBG do not occur, even with dosages of estradiol TTS up to 200 μg per day.[15]

Cardiovascular System. Almost all of the epidemiologic data regarding cardiovascular morbidity and mortality is based on retrospective studies of patients who used oral estrogens, particularly CEE unopposed by progestins. Overall, these data provide evidence for a cardioprotective effect of unopposed oral estrogen.[103] There are no long-term data available, however, regarding the effect of nonoral hormone replacement therapy on cardiovascular morbidity and mortality. There are data available regarding the effect of transdermal hormone replacement therapy on short-term markers that may be associated with cardiovascular status, including lipid profiles and sonographic estimation of vascular resistance and blood flow.

Transdermal estrogen has been demonstrated to raise high-density lipoprotein cholesterol (HDL-C), the cardioprotective lipoprotein, and to lower low-density lipoprotein cholesterol (LDL-C), the atherogenic lipoprotein. These effects, however, are smaller than those seen with oral estrogen, which increases HDL-C by 10% to 29% and lowers LDL-C by 10% to 20%.[77] It is not known whether this difference will mean that the impact of TTS on cardiovascular disease will be less than oral therapy, given that transdermal administration has a more favorable effect on triglycerides as discussed in a following section.

Beneficial effects on the cholesterol profile have not been demonstrated in all studies with transdermal estradiol (Table 1). It appears that transdermal estrogen will reliably produce changes in lipids only in studies of greater than 3 to 6 months duration, as suggested by Lobo.[61] It has also been suggested that parenteral estrogens will not lower LDL-C if serum estradiol levels are less than 120 pg/mL,[118] but will decrease LDL-C if estradiol levels are above 200 pg/mL. Several recent studies, however, have demonstrated statistically significant decreases in LDL-C at sustained estradiol concentrations of less than 120 pg/mL.[19, 81, 104] Lipid effects have also been shown in studies using TTS 50 in which the estradiol concentrations were not stated, but are typically less than 100 pg/mL.[20, 72, 108] Although there is probably a threshold level of serum estradiol that must be reached in order for parenteral estrogens to have an effect on circulating lipids, these recent studies provide evidence that if treatment is continued for at least 3 to 6 months, the level may be within the range that is also necessary for routine treatment of vasomotor symptoms and maintenance of bone density.

There are several subfractions of HDL-C. The HDL_2 subfraction is probably the most important for cardioprotection,[75] and it is the primary fraction increased by oral estrogen therapy.[118] Several studies have demonstrated a significant increase in HDL_2 with transdermal therapy.[72, 118] In other studies of transdermal estrogen in which total HDL-C has decreased significantly and information regarding subfractions is available, the drop has been shown to be largely in the HDL_3 subfraction, which probably has little impact on the development of cardiovascular disease, whereas levels of HDL_2 remained unchanged.[20, 108]

Table 1. EFFECTS OF THE ESTRADIOL TRANSDERMAL THERAPEUTIC SYSTEM ON CIRCULATING LIPOPROTEIN LEVELS

Reference	N	Duration	Dose E_2 (μg)	Progestin	E_2(pg/mL)	Percentage Change From the Baseline			
						Total	HDL-C	LDL-C	TG
Cagnacci, 1991[9]	40	3 months	50	MPA 5 mg 12 d/mo	43	−2	+14	—	−4
Chetkowski, 1986[15]	23	28 days/dose	25–200	—	25–110	−(0–6)	−(3–6)	−(0–6)	−(2–12)
Cortellaro, 1991[19]	20	4 months	50	MPA 10 mg 8 d/mo	81	−6*	−11	−5*	−14
Crook, 1992[20]	30	6 months	50	NEA 0.25 mg transderm 14/28 d	not stated	−11*	−9*	−11*	−23*
Keller, 1992[56]	10	6 months	50	NEA 0.25 mg transderm continuous	46	−4	−11	−17	−6
Marchesoni, 1991[67]	46	18 months	50	MPA 10 mg 12 d/mo	not stated	+4	+5*	—	−10*
Mattson, 1993[72]	52	4 months	50	MPA 5 mg 14/28 d	not stated	−4*	−2	−5*	−8*
		4 months (total 8 month crossover)	100	MPA 5 mg 14/28 d		−6*	0	−7*	−16*
Pang, 1993[81]	29	96 weeks	100	(15 pts took MPA)	115	−6*	−1	−8	−20
	28	96 weeks	100	MPA 10 mg 12/28 d	96	−10*	−12	−11*	−14
Stancyzk, 1988[104]	10	24 weeks	100	—	89	no Δ	+19*	−14	no Δ
Stevenson, 1993[106]	31	6 months	50	NEA 0.25 mg transderm 14 d/month	not stated	−12*	−8*	−11*	−18*
Walsh, 1991[118]	9	6 weeks	100	—	88	−1	+23 HDL-2* −5 HDL-3	−4	0

*Statistically different from baseline as reported by the authors at $P < 0.05$.

Cholesterol values are presented as percentage change from baseline to last value obtained in the study.

Timing of estradiol measurements relative to a dose of estrogen varied between studies. Some percentage changes were estimated from graphs.

E_2 = estradiol, MPA = medroxyprogesterone acetate, NEA = norethindrone acetate, Total = total cholesterol, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides.

In contrast to oral estrogens, which raise serum triglycerides, transdermal patches have been demonstrated to lower serum triglycerides.[20, 67, 72, 108] Once again, the effect was not seen in all studies but was reported in studies of shorter duration and with lower serum estradiol levels than those that produced effects on HDL-C and LDL-C. When progestins were given cyclically with oral estrogens, triglyceride levels were elevated during the estrogen-only phase and were reduced below baseline in the estrogen-progestin phase.[20] In contrast, transdermal therapy lowered triglycerides during both estrogen-only and combined phases. Although the elevation in triglycerides produced with oral therapy does not typically bring the serum level out of the normal range and is probably not clinically significant in the presence of a normal HDL, nonoral administration is recommended for women with familial hypertriglyceridemia or elevated triglycerides from other causes. The reduction of triglycerides by transdermal estradiol may be quite important as there is some evidence that elevation of triglycerides is an independent risk factor for cardiovascular disease in postmenopausal women.[14]

There is growing evidence that the relationship between cholesterol and cardiovascular disease is more complex than increased risk from LDL-C and cardioprotection from HDL-C. Subfractions of cholesterol as noted previously, triglycerides and phospholipids of various types, apolipoproteins A-I and B, and oxidation states of LDL are probably important in determining cardiac risk.[61] Little information is available regarding the effects of parenteral estrogens on these aspects of the lipid profile. While the levels of apoproteins A-I and B fell in one study,[20] two other studies essentially found no changes, with nonsignificant increases in apo A-I and nonsignificant decreases in apo B.[56, 67]

Although the effect of estrogen on cholesterol levels is important, there are likely other effects of estrogen on the cardiovascular system. A study by the Lipid Research Clinics determined that only 50% of the cardioprotective effect of estrogen can be attributed to its effect on serum cholesterol levels.[8] The finding that menopause either has no effect on HDL-C or produces a slight decline in HDL-C[61] suggests that the large increase in cardiovascular disease at the time of menopause is not due primarily to a drop in HDL. It is possible that estradiol exerts a direct effect on blood vessels.[91] Estrogen receptors have been identified in human blood vessels. Estrogen may modulate the synthesis, secretion, or effect of vasoactive mediators or alter cholesterol metabolism within the vessel wall. If further research confirms that factors other than cholesterol are important in the cardioprotective action of estrogen, then it is likely that transdermal estrogen will reduce cardiovascular morbidity and mortality even if its impact on cholesterol levels is not as great as the pharmacologic effect of oral estrogens.

One way of determining the direct effect of estradiol on blood vessels is by Doppler measurement of pulsatility index and other parameters of blood flow. The pulsatility index is thought to represent impedence to blood flow distal to the point of sampling and is thus a measure of arterial tone. Transdermal estrogen given to postmenopausal women reduces the pulsatility index of the uterine artery[5] and the internal carotid artery.[41] Transdermal as well as oral estrogens improve aortic blood flow.[83] Although these findings probably represent beneficial effects of estrogen, whether these measurements can predict cardiovascular risk is not known.

Multiple studies have shown that transdermal estrogen has no effect on clotting factors.[15, 19, 80, 81] For example, Chetkowski et al[15] demonstrated that transdermal estradiol in dosages up to 200 μg/day did not elevate renin substrate or change levels of the clotting factors fibrinopeptide A, high-molecular weight fibrinogen, antithrombin III activity, or antithrombin III antigen.

For most patients, the elevations in renin substrate and clotting factors and reduction in antithrombin III produced by oral estrogen are not clinically significant. It is unusual for normal postmenopausal women to develop hypertension on estrogen replacement therapy. Likewise, transdermal estrogen does not raise blood pressure and, in fact, may lower blood pressure.[81] There is no clinical evidence that oral estrogen replacement increases the risk of thromboembolism in normal postmenopausal women.[24] Because oral therapy, however, elevates renin substrate and clotting factors whereas transdermal therapy does not, it may be prudent to use transdermal estrogens in patients with a tendency toward hypertension or thrombosis.

Skeletal System. Multiple studies using biochemical markers of bone metabolism and several studies employing bone density measurements have demonstrated a protective effect of transdermal estrogen comparable to oral therapy.* A daily dose of 50 μg of transdermal estradiol seems to be as effective as daily oral CEE 0.625 mg or estradiol 1 to 2 mg. For example, in a 2-year, randomized, double-blind, placebo-controlled trial of 93 postmenopausal women, transdermal estradiol 50 μg/day maintained bone density and 100 μg/day increased bone density.[33] A dosage of 25 μg/day reduced bone loss, but was not sufficient to preserve bone density completely. Patients with lower starting bone densities responded most favorably to treatment.

One recent study suggests that transdermal estrogen prevents fractures in women with established osteoporosis.[64] In this double-blinded, randomized, placebo-controlled trial, 75 women with vetebral fractures were given either placebo or TTS 100 μg daily for 1 year. The transdermal therapy preserved bone density and decreased bone turnover. There were fewer fractures in the treated group (relative risk 0.39, 95% confidence interval 0.16 to 0.95) compared with the placebo group.

Vasomotor Symptoms. Transdermal estradiol is as effective as oral therapy for the relief of vasomotor symptoms.[84, 116] A daily dose of 50 μg or higher suppressed the occurrence of hot flashes as assessed by symptoms and objectively by skin thermography.[48, 106] The new transdermal patches employing the matrix system are as effective for vasomotor symptoms as the current reservoir patches.[115] Transdermal therapy may be considered when vasomotor symptoms do not respond to oral therapy.

Vaginal Cytology. Transdermal estrogen is an effective treatment for vaginal atrophy.[15, 17, 80] With menopause, the percentage of parabasal cells increases while the percentage of superficial cells decreases compared with average premenopausal values. Transdermal estrogens increased superficial and decreased parabasal cells. The effects of 50 and 100 μg of transdermal estrogen patches corresponded to 0.625 and 1.25 mg of oral CEE.[15] The matrix system patch is as effective as the currently used reservoir patch for treatment of urogenital symptoms.[115]

Carbohydrate Metabolism and Bile Production. Cyclic administration of a combined estradiol and progestin patch (estradiol 50 μg/day for 14 days followed by a patch that delivered daily estradiol 50 μg/norethindrone acetate 250 μg for 14 days) produced no adverse changes on carbohydrate metabolism as assessed by an intravenous glucose tolerance test.[46] Estradiol-TTS 50 appears to exert beneficial effects on carbohydrate metabolism[10, 108] including reduction in fasting insulin levels, increased insulin clearance by the liver, and increased pancreatic islet response to glucose as assessed by levels of C-peptide.

Biliary cholesterol saturation index and risk of gallstone disease is increased

*References 1, 9, 33, 34, 64, 67, 81, 87, 108.

with oral conjugated estrogen replacement. Oral estradiol 2 mg/day also increases the cholesterol saturation index, particularly in patients with markedly elevated serum estrone.[117] In contrast, transdermal estradiol 100 μg/day does not induce lithogenic bile.[117]

Endometrium. Cyclical transdermal estradiol 50 μg daily unopposed by progestin induced endometrial proliferation and irregular bleeding in many patients.[120] Mild hyperplasia has been reported after only 6 weeks of unopposed TTS 50.[48] Most gynecologists recommend a progestin to produce a regular bleeding pattern and to prevent endometrial hyperplasia. There have been several studies done to determine the appropriate dose of progestin to prevent endometrial hyperplasia, but the minimum doses necessary to oppose each dose of transdermal estradiol are not yet definitively determined.

In patients receiving the 100 μg patch, hyperplasia was prevented in nearly all patients by oral medroxyprogesterone acetate 10 mg daily for 12 days per cycle.[17] In a multicenter trial of TTS 50,[37] no women developed hyperplasia with 0.1 to 1 mg of oral cyclic norethindrone acetate, but the authors of the study recommended the 1 mg dose to account for patient variation in response to the progestin. A combined patch that releases 50[37] μg of estradiol and 250 μg of norethindrone prevented hyperplasia when administered in a cyclic or a continuous fashion in three studies.[56, 59, 119] Because the risk of endometrial hyperplasia must be balanced against the negative impact of these progestins on circulating lipids, 12 days of oral medroxyprogesterone acetate 5 to 10 mg and oral norethindrone acetate 250 to 500 μg are probably appropriate doses for most patients using the 50 or 100 μg estradiol patches. Combined patches of estradiol and norethindrone are not yet available in the United States. As with oral estrogen replacement therapy, patients with irregular bleeding while using transdermal estrogens should have an endometrial biopsy.

Side Effects. Skin irritation is the most common problem associated with the reservoir patch, occurring in 5% to 30% of patients[37, 116] depending on the climate and on individual sensitivity. Skin irritation tends to occur more frequently in hot, humid weather. In a review of placebo-controlled studies (with a total of 448 patients), Utian[116] reported that skin reactions occurred in 24% of patients, but only 4% of patients discontinued therapy because of the skin irritation. Skin reactions may include erythema, itching, discomfort, edema, vesicular rash, induration, and residual pigmentation.[73] Patches may also fail to stay in place on the skin. In studies conducted by the manufacturer, the estradiol-TTS did not show a potential for inducing phototoxicity, photocontact allergy, sensitization, or proliferation of bacteria under occlusion.[116] There has been one case report of hyperpigmentation occurring at the site of a transdermal patch in a menopausal woman who was being treated for pruritus with ultraviolet light.[16]

Regular rotation of the site of application and application to the buttocks reduces the incidence of skin irritation.[21] In some cases, changing the application site each day may overcome skin irritation. The waistline should be avoided, because clothing may rub the system. Although the patch typically stays in place during bathing, if a patch does fall off, the same system may be reapplied to another site and the original treatment schedule continued.

In a randomized, nonblinded study comparing the new matrix system patch with the current reservoir patch,[115] the new patch adhered significantly better. Skin reactions more serious than reddening and itching occurred in 10% of the patients using the conventional patch compared with 5.6% of patients using the matrix system patch. This difference approached but did not achieve statistical significance ($P = 0.07$).

Nausea is less frequent with the estradiol-TTS than with oral therapy. Other systemic side effects associated with oral estrogen replacement, such as breast discomfort, may occur with the transdermal route of administration.

Conclusion

The estradiol transdermal therapeutic system is a good alternative for women who prefer not to take oral medication each day, who absorb oral medications poorly owing to gastrointestinal disease, who have nausea with oral therapy, or who have vasomotor symptoms unresponsive to oral therapy. Transdermal systems deliver the principal estrogen made by the ovary, estradiol, in a continuous fashion, produce physiologic estrone and estradiol levels, and bypass hepatic first-pass effects. Hormone administration can be initiated, discontinued, and adjusted easily. There are no long-term data regarding the effect of transdermal estradiol on cardiovascular morbidity or mortality, but this route of therapy probably has favorable effects on circulating lipids, though less marked than with oral therapy. In contrast to oral estrogens, which raise triglycerides, transdermal estradiol lowers triglycerides. Transdermal estradiol is a good choice for women with elevated triglycerides, and possibly for women with a tendency toward hypertension or thrombosis. Transdermal estradiol is as effective as oral therapy for prevention of osteoporosis. With transdermal estrogen, there is a possibility of endometrial hyperplasia, which can be prevented by administration of a progestin. The possibility of skin irritation and poor adhesion are the principle drawbacks of the transdermal system. Skin irritations can be minimized by rotating the site of application, by applying the patch to the buttocks, and possibly in the future by using a matrix system patch.

Percutaneous Estradiol Gels

Description/Pharmacokinetics

A gel in which estradiol has been dissolved is available in countries other than the United States (Oestrogel). The usual daily dose is 1.5 to 3 mg of estradiol which is dissolved in 2.5 to 5 g of the gel. Patients apply the gel over a large area of the abdomen and thighs and allow the gel to dry for 2 to 3 minutes before allowing clothing to come in contact with the skin. The gel has no odor and does not leave a sticky sensation. This preparation uses the skin as a reservoir for estradiol,[99] in contrast to the TTS, which maintains the estradiol reservoir within the patch.

Serum levels of estradiol are approximately 70 pg/mL for 1.5 mg and 70 to 110 pg/mL for 3.0 mg of percutaneous gel spread over the abdomen and thighs,[4, 22, 26, 29, 94] similar to estradiol levels achieved with 2 mg of oral estradiol.[22, 94] It is important to note, however, that absorption of estradiol depends on the surface area over which it is applied, and therefore accurate dosing may be difficult. In one study, doubling the dose of estradiol did not double the serum levels, probably because the two doses were applied over the same surface area.[94] As with other forms of parenteral estrogen, estradiol gel elevates estradiol to greater degree than estrone, and consequently produces a ratio of estrone to estradiol that more closely mimics the ratio in premenopausal women than does oral therapy.

Effects of Percutaneous Estradiol Gel

Gonadotropins and Binding Globulins. Three milligrams of daily percutaneous estradiol gel reduced FSH levels producing an effect similar to that of oral estradiol at 2 mg.[4, 22] The same dose of estradiol gel either did not alter levels of SHBG[22, 51] or produced a small increase, not as great as that seen with oral therapy.[11, 28] Percutaneous estradiol has no effect on antithrombin III activity or antigen.[22]

Cardiovascular System. Studies have demonstrated a tendency for percutaneous estradiol to increase HDL-C, but in all but one case, the increase did not achieve statistical significance (Table 2). Most of these studies were shorter than 3 months duration, and as discussed with TTS, it may take longer than 3 months to measure an effect on circulating lipids. In one study, percutaneous estradiol increased HDL_2, but the beneficial effect was prevented by oral micronized progesterone.[76] Percutaneous estradiol has been demonstrated to decrease serum triglycerides[4] and LDL-C. Blood pressure and plasma renin substrate were not altered with 2 years of estradiol percutaneous gel at a dosage of 3 mg per day.[49]

Skeletal Effects. In a 2-year study, percutaneous estradiol gel in a daily dosage of 3 mg protected against loss of bone density that was seen in a placebo group and decreased bone turnover as assessed by biochemical markers.[89]

Vasomotor Symptoms, Vaginal Cytology, and Skin Irritation. Percutaneous estradiol 1.5 to 3 mg daily is an effective treatment for vasomotor symptoms.[4, 22, 58] A dosage of 1.5 mg daily on the abdomen and thighs improves vaginal cytology.[58] Local skin irritation is not typically seen with estradiol gel. Estradiol gel produces fewer cutaneous reactions than the reservoir patch, particularly in hot, humid climates.[97]

Conclusion

Percutaneous gel applied over the abdomen and thighs is efficiently absorbed and provides physiologic estrone and estradiol levels. Absorption depends, however, on the surface area over which the gel is applied, and serum estradiol levels may be variable. Estradiol gel has little or no effect on production of binding globulins, clotting factors, or renin substrate. Beneficial effects on lipids and bone have been suggested by a few studies but have not been definitively established. Gels are an effective treatment for vasomotor symptoms and vaginal atrophy. Because they do not involve adhesives or occlusion of the skin, gels produce much less skin irritation than transdermal patches. Percutaneous estradiol gels are not currently available for clinical use in the United States.

VAGINAL AND INTRAUTERINE ROUTES OF ADMINISTRATION

Although vaginal administration of estrogen is used primarily to treat symptoms of urogenital atrophy, significant systemic absorption does occur. Serum estrogen levels and systemic effects depend on the vehicle by which estrogen is administered, the dose, and the type of estrogen. Like with other forms of parenteral estrogen replacement, the first-pass effect on the liver is avoided.

Table 2. EFFECTS OF ESTRADIOL GEL ON CIRCULATING LIPOPROTEIN LEVELS

Reference	N	Duration	Dose E_2 (mg/d)	Progestin	E_2(pg/mL)	Percentage Change From the Baseline			
						Total	HDL-C	LDL-C	TG
Basdevant, 1983[4]	20	2 months	3	—	79	+1	+5	no Δ	−14*
de Lignieres, 1986[22]	10	2 months	3	—	67	no Δ	+3	+4	−18
Elkik, 1982[26]	10	21 days	3	—	80	—	—	—	−14
Fahreus, 1983[29]	17	6 months	3	—	108	—	+4	—	—
Jensen, 1987[53]	20	2 years	3	progesterone 200 mg po 12/28 d second year	~200	−7*	+4	−12*	no Δ
Moorjani, 1991[76]	16	24 weeks	1.5	—		−4	+11*	−6	−1
	16	24 weeks	1.5	progesterone 200 mg po 14/28 d		−3	−6	−3	+8

*Statistically different from baseline as reported by the authors at $P < 0.05$.
Cholesterol values are presented as percentage change from baseline to last value obtained in the study. Some percentages were estimated from graphs.
E_2 = estradiol, total = total cholesterol, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides.

Vaginal Creams

Creams containing CEE (Premarin), 17β-estradiol (Estrace), estropipate (Ogen) (formerly piperazine estrone sulfate) or dienestrol (Dienestrol), a synthetic, nonsteroidal estrogen, are currently available in the United States for vaginal application.[82] Estriol vaginal cream is available in other countries (Ovestin). Concentrations per gram of cream are as follows: CEE, 0.625 mg; estradiol, 0.1 mg; estropipate, 1.5 mg; dienestrol, 0.01 mg; and estriol, 0.1 mg. Because they are used most commonly, discussion focuses on CEE and estradiol.

Pharmacokinetics

Systemic absorption of vaginal estrogen is dependent upon the vehicle or matrix used to deliver the estrogen. If a solution is made by suspending estrogen in saline, absorption is efficient and rapid, but serum estradiol levels are maintained for fewer than 6 hours.[93] When estrogen is formulated as a cream, its absorption is less efficient but more sustained than when in solution (Fig. 4).[88] Therefore, only creams are used clinically. Estrogen administered as a vaginal cream will produce serum estradiol levels that are about one fourth of those produced by oral ingestion of the same dose.[45, 66, 88]

The circulating levels of estradiol and estrone achieved with vaginal estrogens also depend on the particular estrogens that are administered. Estradiol is lipophilic and well absorbed, whereas CEE, which is largely estrone sulfate, is

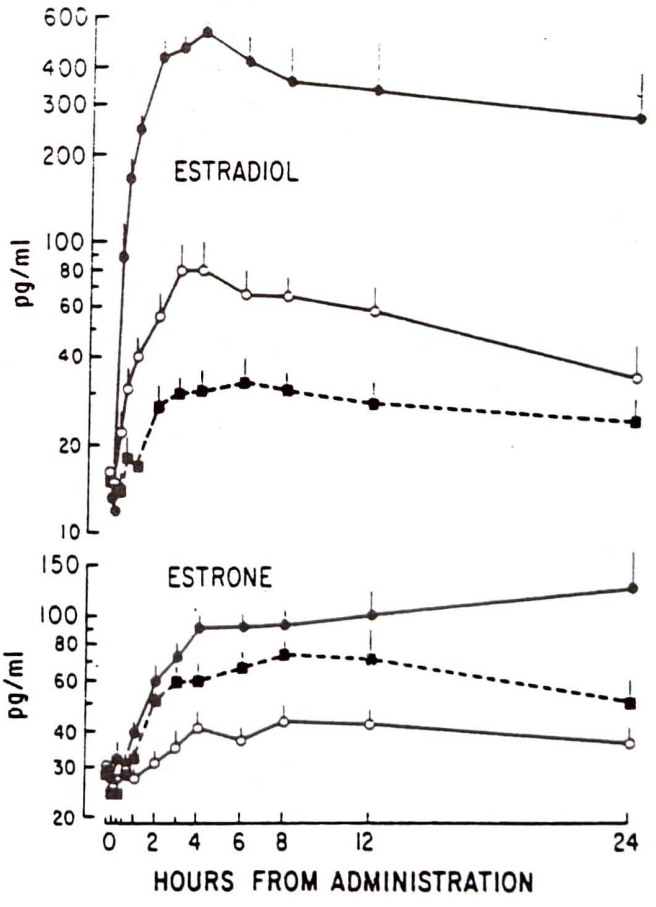

Figure 4. Basal serum concentrations (mean ± SEM) of estradiol (E_2) and estrone and their incremental changes after intravaginal application of E_2 2.0-mg and 0.2-mg doses as compared with 1.25 mg of conjugated estrogen cream in six hypogonadal women with severe estrogen deficiency. ● = 17β-E_2 (2.0 mg), ○ = 17β-E_2 (0.2 mg), ■ = conjugated estrogen (1.25 mg). (Note that estrogen concentrations are plotted on a log scale.) (*From* Rigg LA, Hermann H, Yen SSC: Absorption of estrogens from vaginal creams. N Engl J Med 298:195, 1978; with permission).

more polar and not as well absorbed. In contrast to absorption through the intestine, there is little metabolism of estradiol as it passes through the vagina.[88,93]

Effects of Vaginal Estrogen Cream

Gonadotropins, Hepatic Globulins, and Lipoproteins. CEE formulated as cream produced dose-dependent decreases of up to approximately 30% for both LH and FSH at a dosage of CEE 2.5 mg/day,[66] comparable to the effect of 0.625 mg of oral CEE. Decreases in gonadotropins were greater for estradiol cream at doses of 0.2 mg or 2 mg than for vaginal CEE 1.25 mg.[88] In contrast, vaginal CEE produced greater hepatic effects than vaginal estradiol.[11] Vaginal administration of CEE elevated SHBG, TBG, and renin substrate, but not CBG.[66] With a dose of 2.5 mg, vaginal CEE produced hepatic effects similar to 0.15 to 0.625 of oral CEE. No significant effect was seen on circulating lipids for dosages of vaginal CEE up to 2.5 mg daily for 4 weeks.

Skeletal System. CEE at dosages of 1.25 mg or 2.5 mg per day lowered urinary Ca/Cr ratio but did not alter urinary OHPr/Cr ratio.[66] Because of difficulty with accurate dosing and the lack of data demonstrating its efficacy, vaginal estrogen administration is not a reliable treatment for prevention of osteoporosis.

Vaginal Cytology. Vaginal administration of estrogens is a very effective treatment for vaginal atrophy. Mandel et al[66] showed that vaginal administration of CEE in a daily dosage of 0.3 mg (0.5 g of cream) for 4 weeks produced vaginal cytology similar to that of premenopausal women in the follicular phase, with minimal elevation of circulating estrone and estradiol levels. The vaginal effect was similar to that produced by 1.25 mg of oral CEE, suggesting that the potency of vaginally administered CEE on the vaginal epithelium is fourfold greater than that of the oral route. In a dose-response study, Dyer et al[25] determined that the minimum daily dosage of CEE required to induce premenopausal vaginal cytology was 0.1 mg/day. These doses are much lower than the 1.25 to 2.5 mg daily dosage (2 to 4 g of cream) of CEE recommended by the manufacturer.[82] The doses of vaginal estradiol recommended by the manufacturer (0.1 to 0.4 mg) are in the low range of the doses used in the study of vaginal estradiol discussed previously.

Because vaginal epithelium will respond to very small doses of estrogen, low doses can be used in an effort to correct vaginal atrophy while minimizing systemic absorption. Mandel et al[66] suggested that low doses of vaginal CEE (0.3 mg) can probably be prescribed safely to women with liver-related contraindications to estrogen replacement such as liver impairment or gallbladder disease, given that this dosage is well below the threshold required to produce measureable effects on hepatic function. Very low doses of estradiol cream may also be safe for similar patients. The safety of these recommendations has not been verified in a clinical trial. Use of vaginal estrogen in other situations in which oral estrogen is contraindicated is not advised, owing to systemic absorption.

To treat vaginal atrophy, 3 to 4 weeks of daily estrogen are needed to mature the epithelium, followed by administration of a similar dose once or twice a week to maintain the epithelium. If any therapy is used daily for longer than 4 to 6 weeks, the epithelium may actually became less well estrogenized, possibly because of a loss of sensitivity of the vaginal epithelium.[25] Dyer et al[25] suggested that lack of symptomatic relief may be better managed by discontinuing treatment for a short time and then restarting at a lower dose, rather than continuing to increase the dose.

Estriol vaginal cream (Ovestin) is also an effective treatment for vaginal atrophy.[57] However, some systemic absorption occurs, as suggested by slight suppression of gonadotropins. Estriol offers little advantage over other vaginal estrogens that are currently available.

Endometrium. Because estrogen is absorbed from vaginal CEE and estradiol, this route of delivery carries a risk of endometrial cancer. Moderate estrogen effects on the endometrium have also been demonstrated with intravaginal estriol and dienestrol.[121]

Conclusion

Vaginal estrogen cream is an effective treatment for vaginal atrophy. Because vaginal cream is absorbed into the systemic circulation, this route carries a risk of endometrial hyperplasia and should not be used in most situations in which oral estrogen therapy is contraindicated. Vaginal estrogen creams are not recommended for prevention of cardiovascular disease or osteoporosis owing to variable absorption and the paucity of studies demonstrating beneficial effects.

Vaginal Rings

Vaginal rings were first designed for contraception but have been tested clinically as a vehicle for hormone replacement.[112] Rings are made by mixing pure crystalline 17β-estradiol with a biologically inert polymer. Levonorgestrol may be delivered along with estradiol using a vaginal ring.[32, 35]

Absorption depends in part on the surface area of the ring. After an initial burst of serum estradiol, the 100-mg ring produces sustained estradiol levels of approximately 45 to 55 pg/mL; the 200-mg ring, levels approximately 70 to 100 pg/mL; and the 400-mg ring, levels of approximately 120 to 150 pg/mL, typical of the follicular phase of the menstrual cycle. These levels can be maintained in a fairly constant fashion for up to 3 months using a single ring.[113] Estradiol is absorbed with little metabolism in the vaginal wall; therefore, physiologic estrone to estradiol ratios are achieved. Estradiol levels fall rapidly when the system is removed.

Vaginal rings are noninvasive and easily removed. Rings, which are up to 55 mm in diameter, are placed in the upper third of the vagina, are maintained in place by the pressure of the vaginal walls, and stay in the vagina during exercise or straining. They are typically removed before intercourse and replaced afterward. The rings may be removed periodically for cleaning and vaginal hygiene. Rings are not available for clinical use in the United States.

Little information is available regarding the systemic effects of vaginal rings. The combined estradiol and levonorgestrel systems ring produced reduction in LDL-C, very low-density lipoprotein cholesterol (VLDL-C), HDL-C, and triglycerides, suggesting that the progestin effect was dominant.[32, 35] Bone turnover was decreased as assessed by biochemical markers.[32]

Vaginal Tablets

Vaginal tablets containing 25 μg of estradiol (Vagifem), 6 mm in diameter, are inserted into the vagina with a disposable applicator and can be easily removed. Vaginal estradiol tablets are an effective treatment for vaginal atrophy[71, 74] and produce minimal endometrial effects when given in twice weekly dosages of 25 μg. They are not available in the United States.

Intrauterine Devices

A T-shaped intrauterine device that releases levonorgestrel has recently been studied in postmenopausal women.[2] An advantage of this device is that it deliv-

ered the highest concentration of progestin locally in the uterus, where it is desired. It also eliminated the need for oral progestin, produced amenorrhea in 15 of 18 women who were taking oral estradiol, and will last for 5 years. However, effects on the cardiovascular and skeletal systems have not yet been examined in postmenopausal women.

Implants

Description/Pharmacokinetics

Crystalline implants of estradiol are used in the United Kingdom, Australia, and South Africa; there are 200 licensed users in the United States.[111] These small biodegradable pellets are injected subcutaneously into the abdominal wall or buttock using local anesthesia in a procedure that takes about 5 minutes. Insertion of the pellet may produce local bruising, bleeding, and occasionally the pellet may extrude; but skin reactions like those seen with transdermal therapy do not occur. A disadvantage of implants is that it is not easy to adjust doses or discontinue treatment, as the pellets are very difficult to remove. Implants, however, have advantages of providing stable circulating estrogen levels and relieving the patient of the need to take a daily pill.

Implants of standard sizes (25, 50, and 100 mg) produce higher sustained levels of estradiol than any other route of estrogen replacement. Sustained serum estradiol levels for 25, 50, and 100 mg pellets are 40 to 70, 80 to 120, and approximately 150 pg/mL respectively.[62, 79, 102, 104, 114] The levels for a single 25-mg pellet are similar to those for a 50 μg patch and comparable to follicular phase levels in cycling women. There is limited metabolism of estradiol to estrone in the skin and hepatic conversion of estradiol to estrone is less than with oral therapy because no first-pass effect occurs in the liver. As a result, physiologic estrone to estradiol ratios are achieved.[62, 79, 114]

After implantation, no initial burst to high estradiol levels occurs.[62] Estradiol concentrations rise to a peak at 1 to 2 months, plateau for 2 to 4 months, then gradually decline (Fig. 5).[114] As with other routes of administration, there may be significant variation in serum estradiol levels between patients, with a threefold to fourfold difference between the highest and lowest values in several studies.[3, 62, 79] Implants, however, provide more stable circulating estrogen levels than any other route of administration.[62, 104]

Successive implants may have a cumulative effect of raising estrogen levels, occasionally to sustained levels as high as those produced in the periovulatory phase by cycling women.[111] Garnett et al[43] found a mean estradiol level of 207 pg/mL in 1388 women who received multiple implants of 50 or 100 mg. Barlow et al[3] determined that when 50 mg estradiol implants were given every 6 months, the mean estradiol at 36 months (181 pg/mL) was significantly higher than at 6 months (109 pg/mL), suggesting an accumulation of estradiol with repeated implants. The clinical significance of sustained high estrogen levels is unknown. Although no studies have demonstrated detrimental effects, we are unaware of any long-term studies that have specifically examined the impact of high estrogen levels on the development of clinical disease such as breast cancer. Because the goal of estrogen replacement is to mimic normal ovarian production of estrogen as closely as possible, the dose should be reduced to a maintenance level of 25 to 50 mg every 6 months when successive implants are administered.[111]

Testosterone implants may be placed at the same site as the estrogen. These implants are an effective treatment for loss of libido in some menopausal women.[6, 111] In contrast to 17-alkylated oral testosterone, which is potentially

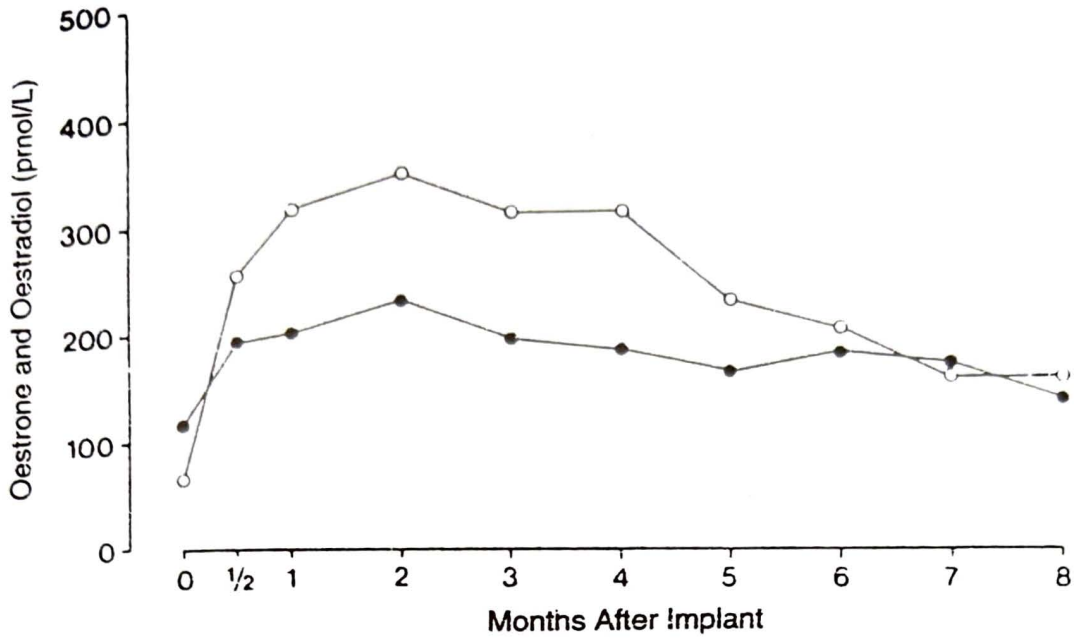

Figure 5. Mean concentrations of estrone and estradiol in peripheral plasma following an implant of estradiol (50 mg). Note that concentrations are expressed in pmol/L. ○ = estradiol, ● = oestrone. (*From* Thom MH, Collins WP, Studd JWW: Hormonal profiles in postmenopausal women after therapy with subcutaneous implants. Br J Obstet Gynaecol 88:426, 1981; with permission, Blackwell Scientific Publications Limited.)

hepatotoxic, an implant of testosterone is not associated with liver toxicity, and virilization is rare.[111]

Effects of Estradiol Implants

Gonadotropins and Binding Globulins. Implants produce suppression of FSH levels into the premenopausal range, an effect which is greater than with any other form of estrogen replacement. This is because with the pellet, serum estradiol levels are higher and fluctuate less than with other routes of administration. The 100 mg implant produces 90% suppression of FSH levels and the 50 mg implant produces an approximately 60% decrease.[114] Suppression of LH is less dramatic. The nadir in gonadotropins is reached at 2 to 3 months, but gonadotropins remain in the premenopausal range for up to 6 months.[114] Levels of SHBG and CBG did not change with 25 mg estradiol pellets.[62]

Cardiovascular System and Carbohydrate Metabolism. Implants increase HDL-C and less consistently lower total cholesterol and LDL (Table 3). In general, the effects are less dramatic than seen with oral estrogen but are in a favorable direction. All of these studies are at least 3 months in length, which may in part explain why these studies demonstrated effects on cholesterol profile while some of the transdermal studies did not. In addition, estradiol levels in these studies were less likely to drop below 40 to 50 pg/mL, and on average were higher than in the studies with transdermal estrogen. The effects of estradiol implants on Doppler assessment of blood flow and on long-term cardiovascular morbidity and mortality have not been reported. Carbohydrate and insulin metabolism are unaffected by a single 25 or 50 mg estradiol implant as assessed by a 100 g 2-hour glucose tolerance test.[78]

Skeletal System. Several studies have demonstrated the ability of estradiol

Table 3. EFFECTS OF ESTRADIOL IMPLANTS ON CIRCULATING LIPOPROTEIN LEVELS

Reference	N	Duration	Dose E_2 (μg)	E_2 (pg/mL)	Percentage Change from the Baseline			
					Total	HDL-C	LDL-C	TG
Farish, 1984[32]	14	6 months	50	100	−3	+7*	−6	−8
	17	6 months	50 + 100 mg T	91	−5*	+4	−8*	−14
Lobo, 1980[62]	12	3 months	25	50–70	+20	+50	+3	+20
Notelovitz, 1987[78]	6	6 months	25	70	−8*	−6	—	+20
	6	6 months	50	125	−5	−4	—	−3
Sharf, 1985[98]	8	14 weeks	100	308	−12	+32*	−23*	0
Stancyzyk, 1988[104]	10	24 weeks	50	113	no Δ	+17*	−1	no Δ

*Statistically different from baseline as reported by the authors at $P < 0.05$.
Cholesterol levels are reported as percentage change from baseline to the last value obtained in the study. Some percentage changes were estimated from graphs.
No patient received progestin.
E_2 = estradiol, T = testosterone implant, MPA = medroxyprogesterone acetate, NEA = norethindrone.

implants to maintain or to increase bone density, either when given alone[78] or along with testosterone implants.[44, 92, 110] Administering testosterone along with the estradiol probably does not yield additional benefit with respect to bone density.[3, 42] Doses of 25 to 75 mg every 6 months have been shown to be effective for maintaining bone density, with some tendency toward greater benefit with higher serum levels of estradiol.[110]

Vasomotor Symptoms. Estradiol implants are an effective treatment for hot flushes.[3, 12, 79, 104] It is well documented, however, that vasomotor symptoms may return before the end of 6 months, when estradiol levels are still in the follicular range or higher.[6, 62, 79, 114] It is likely that this recurrence of vasomotor symptoms is due to a slight drop in estradiol levels at 4 to 6 months after administration of an implant. If symptoms occur, the patient may request reimplantation prior to 6 months. However, the interval between implantations should not be shortened, because circulating estradiol may rise to supraphysiologic levels (i.e., within or above the periovulatory range). Furthermore, vasomotor and psychological symptoms may return despite supraphysiologic concentrations of estrogen.[38, 42]

Endometrium. Estradiol implants carry a risk of endometrial hyperplasia and cancer. In addition, the estrogenic effect on the endometrium may persist after implants are discontinued. Endometrial effects have been shown to persist for up to 43 months after the final implant is placed, even when doses of 50 mg roughly every 6 months are given.[39] Therefore, if a patient discontinues estrogen replacement with the implant, it is advisable to give cyclic progestin until no withdrawal bleeding occurs for several months.

A higher dose of progestin is needed with the implant than with other forms of therapy because of higher circulating levels of estrogen. There are few data on the proper dose of progestin to prescribe with various doses of implants. Dydrogesterone, a nonandrogenic progestin, in dosages of 10 mg and 20 mg for 14 days each cycle opposed the proliferative effects of the 50 mg estradiol implant.[86] A dosage of 20 mg for 14 days each cycle produced secretory changes in the endometrium of patients using a 100 mg implant.[47]

Conclusion

Estradiol implants eliminate the inconvenience of taking a pill each day and produce more constant levels of estradiol than any other route of administration. They have been demonstrated to produce favorable changes in circulating lipoproteins, to preserve bone, and to relieve vasomotor symptoms. There are significant disadvantages of subcutaneous implants, including the possible development of supraphysiologic levels of serum estradiol, the possible return of vasomotor symptoms while serum estradiol levels are still in the premenopausal range, the need for a surgical procedure, the inability to adjust doses easily, and the possibility of prolonged endometrial stimulation when the implant is discontinued. In Europe and in other areas of the world outside of the United States where implants are available, however, many women and their physicians use implants despite these possible disadvantages. In fact, many find subcutaneous implants the preferred route of estrogen administration.

OTHER ROUTES OF ADMINISTRATION

Several other routes of administration have been studied but do not appear to offer advantages over the alternatives that have been discussed. Intramuscular injection of estradiol esters such as estradiol cypionate produces variable hormone levels, pain at the site of injection, and necessitates an injection every 2

weeks.[69] With nasal administration of estradiol, serum estradiol and estrone levels rapidly increase but then quickly decline to baseline by 3 hours.[70] Marked variation in serum estrogen levels also occurs with sublingual administration,[7] with very high peak levels at 1 hour after administration.

CONCLUSION

Alternatives to oral estrogen replacement, including the transdermal patch, deliver estradiol in a constant manner, produce more physiologic estrone and estradiol levels than oral estrogens, and avoid the first-pass effect on hepatic protein synthesis. They provide an alternative for women who prefer not to take a daily oral medication, who have nausea with oral therapy, who absorb medications poorly owing to gastrointestinal disease, or who have vasomotor symptoms unresponsive to oral estrogen. Although there are no data available regarding the ability of parenteral estrogens to prevent cardiovascular disease, the transdermal patch has been demonstrated to have favorable effects on lipoproteins and to lower triglycerides. The major side effect of the transdermal patch is skin irritation, which may be minimized as discussed previously. Estradiol percutaneous gels and implants have advantages similar to the patch, but are available only outside of the United States. Vaginal administration of estradiol or conjugated equine estrogen cream is efficacious for treatment of vaginal atrophy but is not recommended for prevention of cardiovascular disease or osteoporosis, and in general should not be used by patients with a contraindication to oral therapy. Other routes of administration, including vaginal rings and progestin-containing intrauterine devices, are other possible options for the future.

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