Topical estrogens: an update

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SUMMARY

Topical estrogens have been used for many different dermatologic conditions. Currently, they have reemerged as a form of estrogen replacement therapy for peri/postmenopausal women. In this article we review current applications and future indications for topical estrogen therapy, with an emphasis on the transdermal estrogen patch.

KEY WORDS

estrogen, estrogen replacement therapy, topical estrogens, transdermal patch

Introduction

The use of topical estrogens has undergone many changes since the pioneering work of Zondek, who in 1936 demonstrated that estrogen could pass percutaneously through intact skin (1). In 1945 he found a clinical application for topical estrogens as an effective treatment for vaginal atrophy in postmenopausal women (2). In the mid-20th century, topical estrogens were used in a variety of dermatological disorders, including acne vulgaris, keratoderma climactericum, hidradenitis suppurativa, seborhea oleosa, male and female-pattern baldness, urogenital (vaginal/vulvar) atrophy and peri/postmenopausal vasomotor complaints (3,4).

One of the authors has conducted numerous clinical trials on the effects of topical estrogen therapy in the treatment of acne vulgaris, keratoderma climactericum and premature alopecia (5-11). Most of these treatments, excluding the use of estrogen creams for treatment of vaginal atrophy, are no longer employed clinically. The new millenium views the role of topical estrogens and the vehicle of application utilized, much differently from half of a century ago. Today, topical estrogen therapy has gained a newfound emphasis in the form of transdermal patches used for hormone replacement therapy in peri and postmenopausal women. We provide a review of the current application for topical estrogens, with an emphasis on the transdermal estrogen patch.

Transdermal Estrogen Patch

Transdermal estrogen patches, or transdermal therapeutic systems (TTSs), are a relatively new treatment modality in estrogen replacement therapy (ERT). Oral estrogens continue to be the mainstay of ERT, but

transdermal estrogen patches have gained popularity in recent years (12). In 1992, 15% of ERT in the United States was in the form of transdermal estrogen patches, while TTSs are the most popular form of estrogen replacement in Great Britain for postmenopausal women who have had a hysterectomy (12,13).

Transdermal estrogen patches consist of reservoir (Estraderm TTS 50®) and matrix (Climara®) patches, which deliver daily doses of 50 to 100 mg of 17b-estradiol (13-16). The matrix patch is applied to the chest or abdomen weekly, while the Estraderm® patch requires biweekly application. Studies have proven that compliance in women undergoing ERT is higher in those who use transdermal patches as opposed to oral estrogen therapy (17,18). Compliance is important in women undergoing ERT, since postmenopausal women may face thirty or more years of therapy.

TTSs bypass the first pass effect through the liver, which is encountered with oral estrogen therapy, allowing lower doses of estrogens to be administered percutaneously (13,15). Large doses of oral estradiol must be taken in order to achieve therapeutic levels and to counter metabolism by the liver and inactivation by the gut wall. A large part of oral estradiol is converted to estrone by the liver, causing an imbalance in the estradiol/estrone ratio which is normally 1:1 in premenopausal women (13,16) In contrast, TTSs are delivered directly to the systemic circulation, allowing for a more physiologic estradiol/estrone ratio (16). In addition, the first pass effect with oral estrogen replacement produces noticeable alterations in hepatic protein synthesis and metabolism (Table 1) (13). While the elevation of these proteins in the bloodstream does not seem to be directly implicated in clinical health consequences, the increased biliary cholesterol saturation index and decreased levels of chenodeoxycholic acid (bile acid that acts to solubilize cholesterol) point to an increased diathesis towards gall stone disease (13,19). Studies have confirmed that the risk of gallstone disease is increased with oral estrogen therapy (20,21). In contrast, transdermal estrogen application shows no appreciable increase in these proteins (13). Oral estrogens also produce fluctuating levels of estradiol and estrone throughout the day, while TTSs produce less fluctuation in serum estradiol levels (13,15). Thus, transdermal estradiol patches offer the advantage of bypassing the first pass effect of the liver, minimally affecting hepatic protein synthesis and metabolism and mimicking ovarian function by delivering physiologic levels of estradiol at a constant rate.

The treatment of choice for menopausal vasomotor symptoms (hot flashes) and vaginal atrophy is estrogen replacement therapy (13). It has proven effective in the treatment of these symptoms (22). In addition to alleviating climacteric symptoms associated with menopause, it has been demonstrated that ERT can enhance and even prolong a postmenopausal woman's lifespan (23). A recent retrospective study has shown that ERT can reduce the risk of cardiovascular disease by 50% (24). Oral estrogen replacement therapy has provided evidence for long-term cardioprotective effect. (13,15). Oral and transdermal estrogens affect the lipid profile (Table 2). Both forms of replacement therapy similarly decrease total cholesterol and LDL (13,15,16). In contrast, TTSs decrease triglyceride levels and maintain HDL levels, while oral estrogens show an increase in triglyceride levels and an increase in HDL levels (13,15, 16). A study of patients receiving transdermal ERT demonstrated increased blood flow and a decreased vascular resistance (25). It has been proposed that estrogen's cardioprotective effect is mainly influenced by its physiologic influence on arterial endothelium and smooth muscle, including enhancement of synthesis of vasodilatory factors (nitric oxide and prostacyclin) and inhibition of vasoconstrictive substances (15).

The second major benefit of estrogen replacement therapy is for osteoeporotic changes in postmoenopausal women. Transdermal estrogen patches have proven effective in maintaining lumbar bone density at 50 mg and increasing lumbar bone density at 100 mg, thus proving as effective as their oral counterparts in preventing and treating osteoporotic changes (16,26). One study showed that oral and transdermal estrogen increased bone density to a similar degree (27).

As summarized, transdermal estrogen patches provide an exciting alternative for estrogen replacement therapy in peri/postmenopausal women for both climacteric symptoms and long-term health benefits. Transdermal estrogen therapy is also indicated in certain medical conditions that preclude oral estrogens, including

Table 1. Metabolic changes seen with ERT[13-16]

	TTSs	Oral Estrogen Replacement
Angiotensionogen	–	↑
Thyroid-binding globulin (TBG)	–	↑
Cortisol-binding globulin (CBG)	–	↑
Sex hormone-binding globulin (SHBG)	–	↑
Growth Hormone (GH)	–	↑
Fibrinogen	–	–
Biliary cholesterol saturation index	–	↑
Chenodeoxycholic acid	–	↓

hypertriglyceridemia, non-response to oral estrogens, oral estrogen-induced hypertension, and high-risk cholelithiasis patients (15).

TTSs have similar systemic side effects as oral estrogens, including the development of breast tenderness, headaches, flushing, fluid retention, and weight gain, nausea and depression (28). Skin irritation is the most frequent adverse side effect encountered with the transdermal estrogen patches (29). Localized dermatologic effects due to patch application include erythema, pruritus, vesicular rash, edema, induration and residual pigmentation (22). Rotation of sites of patch application and application to the buttocks have proven to reduce skin irritation (30).

Endometrial hyperplasia, with possible future carcinomatous change, is a concern in the use of unopposed transdermal estrogen patches (16). Cyclical transdermal application unopposed by a progestin caused endometrial proliferation and irregular bleeding in many patients (31). Addition of an oral progestin is recommended to prevent endometrial hyperplasia, with possible progression to endometrial carcinoma, in women with an intact uterus (16,22).

Other Vehicles of Topical Estrogen Therapy

Percutanous estradiol gels (Oestrogel®) are available for use outside of the United States (22). The gel is applied over the abdomen and thighs and allowed to dry for a few minutes before clothing is worn. Similarly to the transdermal patch, estrogen is absorbed percutaneously into the systemic circulation and provides a physiologic estradiol/estrone ratio (13,22). However, absorption of the gel into the systemic circulation is dependent on the surface area to which the gel is applied; serum estradiol level may thus fluctuate with each application (32). These gels have proven efficacious in treating vasomotor symptoms and vaginal atrophy associated with menopause, but data on cardioprotective and osteoporotic effects are not definitive (13,22).

Table 2. Effects of ERT on the Lipid Profile[13-16]

	TTSs	Oral Estrogen Replacement
Total cholesterol	↓	↓
LDL	↓	↓
HDL	–	↑
Triglycerides	↓	↑

Estrogen-containing creams (Estrace®, Ogen®) for vaginal application are available in the United States (22). Their efficacy in the treatment of vaginal atrophy has been proven (13,22,33). Systemic absorption of the estrogen cream does occur through vaginal epithelium, increasing the risk of endometrial hyperplasia with possible progression to cancer (22). The absorption of estrogen is variable, depending on the type and dose of estrogen and the vehicle by which it is administered (22). For this reason, estrogen creams are not recommended for long-term estrogen replacement therapy.

Vaginal rings contain a mixture of crystalline 17b-estradiol and an inert polymer (13). Vaginal rings are manually placed in the upper third of the vagina and maintain their position by pressure from the vaginal walls. These vaginal rings are easily removed for hygienic purposes. Systemic absorption through vaginal epithelium depends on the surface area of the ring (22). Estradiol levels can be maintained for up to three months (34). Sufficient data has not been published on the efficacy of these rings as an estrogen replacement therapy, and the rings are not currently available in the United States.

Vaginal estradiol tablets (Vagifem®) are manually inserted into the vagina and have proven efficacious in the treatment of vaginal atrophy (35,36). Biweekly dosing has been reported to have negligible systemic and endometrial effects (22). This treatment modality is also not available in the United States.

Crystalline estradiol implants are placed subcutaneously in the abdomen or buttock. Implants provide stable circulating levels of estradiol for a period of 4-12 months (13,37,38). Problems with implants arise from the fact that dosing is not easily adjusted and the possibility of endometrial stimulation even after discontinuation of therapy (22). Implants are used much more frequently for ERT in Europe.

Future Direction

Transdermal estrogen patches that are available in lower dosages, having longer application periods and that are less irritating to the skin will be introduced in the near future. Combination estradiol/progrestin patches are also currently being investigated, but not yet available for clinical use in the United States (39,40). This development would greatly facilitate treatment in women taking estrogen replacement therapy who also need progestin treatment. Estrogen replacement therapy in postmenopausal women is gaining increased emphasis as today's aging population grows. The cardioprotective and osteoporotic effects of ERT have been reviewed.

Other possible areas for use of topical estrogens include cosmetic facial applications in peri/postmeno-

pausal women for the treatment of skin aging and wrinkling. The effects of topical estrogen for this application have not yet been defined, although preliminary studies show promising results (41-43). A decrease in wrinkle depth and an improvement of elasticity and firmness of facial skin was seen after six months of topical application (41). Immunohistochemistry demonstrated an increase in Type III collagen in treated skin, which may explain the clinical picture of increased firmness and decreased wrinkles in these patients (41).

Our initial clinical trials with topical estrogens half of a century ago included the beneficial treatment of keratoderma climactericum (6). It is with great interest that we have found a recent case report in which this condition has been similarly effectively treated with topical estrogen (44).

We have reviewed the current applications of topical estrogens, with an emphasis on estrogen replacement therapy using the transdermal estrogen patch. We are excited that topical estrogens have found important new applications, most of them much different from half of a century ago.

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