Review

Estrogen-deficient skin: The role of topical therapy☆,☆☆

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ABSTRACT

Menopause is a major turning point in a woman's life that is characterized by declining ovarian function and decreased serum estrogen levels. The resulting hormonal changes particularly affect the skin, with postmenopausal symptoms such as loss of structural architecture and increased propensity to damage becoming rapidly noticeable. Interestingly, studies have shown that estrogen deprivation in postmenopausal conditions accelerates many skin changes, including dryness, atrophy, fine wrinkling, and poor wound healing. Thus, the effects of low estrogen on the skin are an important endogenous cause of aging skin in women, yet topical treatment strategies that target cutaneous symptoms are limited. The goal of this article is to provide an overview of the role of estrogen in the skin and changes associated with estrogen deficiency, as well as review alternatives to systemic estrogen therapy and describe the effects of these interventions on cutaneous aging in postmenopausal skin. Specifically, clinical studies that utilize topical estrogens and topical isoflavones, which are soy-derived compounds that interact with estrogen receptors, are discussed.

Contents

Introduction

Increased longevity in today's developed societies is resulting in an ever-expanding elderly population (Wilkinson and Hardman, 2017). Because women are living longer but the age of menopause onset remains stable around the age of 51 years, an increasingly

larger portion of a woman's life is spent in a postmenopausal state (Labrie, 2015). Menopause, defined as the cessation of menstrual periods for 12 months due to permanent loss of ovarian function, results in a sharp decline in estrogen levels (Greendale et al., 1999) and symptoms in nearly every body system (Duarte et al., 2016; Shu and Maibach, 2011).

Postmenopausal symptoms are rapidly noticeable in the skin, which loses its structural architecture and becomes prone to damage (Sator et al., 2004; Wilkinson and Hardman, 2017). Estrogen deprivation accelerates many of the skin changes often attributed to exogenous aging alone, including dryness, atrophy, fine wrinkling, and poor wound healing (Creidi et al., 1994; Irrera et al., 2017). The goals of this article are to provide an overview of the role of estrogen in the skin and changes associated with estrogen deficiency, as well as review alternatives to systemic estrogen therapy and describe the effects of these interventions in estrogen-deficient skin (EDS).

Estrogen-deficient skin

Cutaneous aging is the result of a combination of chronologic, environmental, genetic, and hormonal factors (Shu and Maibach, 2011). Because low-estrogen states and the resulting skin manifestations can be due to iatrogenic causes and because the term "menopausal" does not encompass the broad range in age of women who experience these symptoms, we prefer the term EDS. Estrogens are steroids that are synthesized from cholesterol in the ovary in premenopausal women and in the peripheral tissue postmenopausally (Hall and Phillips, 2005).

Two estrogen receptors (ERs), α and β, have predominantly been identified in the skin (Pelletier and Ren, 2004). Histologically, their relative expression levels start to decline from the perimenopausal years onward as women enter an estrogen-deficient state (Nelson and Bulun, 2001). Both ERs bind to estradiol with similar affinity; however, the expression profiles of ER-α and ER-β are tissue-specific, with ER-β more widely distributed within the skin than ER-α. Interestingly, ER-α activation is a main driver of reproductive cancers (Kumar et al., 2016), which makes the selective targeting of ER-β a promising new avenue for targeted intervention.

Many studies have shown that upon entering menopause, women detect a swift commencement of skin aging symptoms (Thornton, 2013). One of the first symptoms experienced is increased skin dryness, followed by decreased firmness and elasticity (Castelo-Branco et al., 1992). These symptoms correspond with structural and architectural changes, such as decreased sebum production, collagen content, dermal thickness, and elastin fibers (Affinito et al., 1999; Raine-Fenning et al., 2003; Sumino et al., 2004; Verdier-Sévrain, 2007).

Estrogen helps retain and restore skin moisture through the promotion of sebum secretion, primarily by regulating the expression of insulin-like growth factor receptors and increasing the production of insulin-like growth factors from fibroblasts (Ashcroft et al., 1997), which in turn induces lipogenesis in human sebocytes and leads to moisture retention. Additionally, estrogen therapy elevates the levels of mucopolysaccharides and hyaluronic acids in the dermis to keep the skin hydrated (Grosman, 1973; Grosman et al., 1971), which improves the barrier function of the stratum corneum and optimizes the surface area of corneocytes (Duarte et al., 2016).

The progressive decline of skin thickness in EDS is mostly due to the loss of dermal skin collagen (Brincat et al., 1987, 1987) and reduced rates of collagen deposition (Ashcroft et al., 1997). Collagen levels in the skin, with type I (80%) and type III (15%) as the most prevalent (Shah and Maibach, 2001), correlate with estrogen levels (Affinito et al., 1999), and supplementation with both systemic hormone replacement therapy (Castelo-Branco et al., 1992) and topical

estrogen (Creidi et al., 1994; Varila et al., 1995) in estrogen deficiency has been shown to increase collagen synthesis.

Studies have also shown that estrogen deficiency accelerates the loss of skin elasticity by triggering ultrastructural changes in elastin fibers, leading to wrinkle formation (Bolognia et al., 1989). The rate of extracellular matrix deterioration in postmenopausal women correlates more convincingly with estrogen deficiency than with chronologic aging (Brincat et al., 1987, 1987), supporting the role of estrogen in the skin. Studies have shown that up to 30% of dermal collagen may be lost in the first 5 years after menopause, and collagen decreases by approximately 2.1% per year (Archer, 2012). Likewise, skin thickness decreases 1.1% per year.

In addition, experimental data have shown that the presence of estrogen may protect skin cells against oxidative damage, and the dramatic decrease of estrogen levels during menopause could render skin more susceptible to oxidative damage (Bottai et al., 2013). Although the implications of hormonal aging are still being explored, ample evidence indicates that the declining levels of estrogen during menopause are responsible for the characteristic skin changes, namely epidermal thinning, declining dermal collagen content, diminished skin moisture, increased laxity, and impaired wound healing (Hall and Phillips, 2005).

Treatment

Although systemic hormone replacement therapy can reverse signs of EDS, such as skin and vaginal dryness and atrophy, the various risks (mainly hyperplasia or cancer of the endometrium (Sator et al., 2004), and concern regarding increased risk of breast and ovarian cancer) preclude its use to treat skin disorders (Duarte et al., 2016). Because maintaining youthful skin is strongly desired by a large portion of today's population (Jenkins et al., 2014), studies that evaluate approaches to reverse skin changes in menopause through alternative medicine and topical therapy have expanded (Shu and Maibach, 2011).

Methods

We conducted a literature search in the MEDLINE (via PubMed) database from January 1987 to June 2018, combining keywords related to the following topics: "Menopause", "post-menopause", "climacteric", "skin", "topical", "cutaneous", "estrogen", "estradiol", "oestrogen", "oestradiol", "17-beta estradiol", "estrogen cream", "estrogen ointment", "isoflavone", "genistein", and "phytoestrogen." Additionally, a detailed manual search of references from key articles was completed to find studies missed by the computer search.

An investigator reviewed the search results by way of title and abstract screening; articles were included if the abstract described a clinical study of menopausal or postmenopausal women who were treated with either a topical estrogen or topical isoflavone product. Case reports, animal studies, and studies where the majority of participants were men rather than women were not included. Topical products included those described as gel, ointment, cream, patch, or a transdermal application. Additionally, although menopause was defined individually in each study, the criteria were consistent and entailed at least a 6- to 12-month period of amenorrhea.

Results

All clinical studies reporting the results of using either a topical estrogen (Table 1; Ashcroft et al., 1999; Bolognia et al., 1989; Brincat et al., 1987, 1987; Callens, 1996; Castelo-Branco et al., 1992; Creidi et al., 1994; Fuchs et al., 2003; Jemec and Serup, 1989; Masuda et al., 2013; Neder and Medeiros, 2012; Patriarca et al., 2007, 2013; Piérard-Franchimont et al., 1995; Punnonen et al., 1987; Rittié et al., 2008;

Table 1
Studies evaluating the effect of topical estrogen on the skin in postmenopausal women

Study group	Treatment group (n)	N	Treatment length	Treatment Location	Outcome of interest
Brincat et al., 1987, 1987	1.5 mg estradiol gel	16	12 months	Lower abdomen	- Skin collagen content in the abdomen (gel application site) statistically higher compared with baseline - Skin collagen content in the thigh (distant site) increased but did not reach significant levels
Punnonen et al., 1987	1 mg oestriol ointment	14	3 weeks	Lower abdomen	- Elastic fibers in the papillary dermis were thickened, better orientated, and slightly increased in number in 50% of patients compared with 0% of the controls - Epidermal thickness slightly increased in 29% of patients and 17% of controls - No significant change observed in epidermal cell size, epidermal mitotic activity, dermal vascularization, or inflammatory infiltrate in specimens taken before or after the treatment
Bolognia et al., 1989	Transdermal 17beta-estradiol patch (*Estraderm*)	18	6 months	*n/a*	- Frequency of cutaneous flushing was the only cutaneous finding significantly decreased in the treatment group when compared with the placebo group - No significant differences between the treatment and placebo groups for the following cutaneous signs: dryness, scaling, excoriations, bruises, scalp scaling number of lentigines, and number of seborrheic keratosis
Jemec and Serup, 1989	17beta-estradiol gel (0.1 mg/g and 1.0 mg/g concentrations)	8	180 days	Ventral aspect of forearm	No statistically significant differences observed with regard to skin conductance, capacitance, elasticity, distensibility, and hysteresis when estrogen-treated areas were compared with placebo-treated areas
Castelo-Branco et al., 1992	50 ug/day transdermal 17beta-oestradiol	28	12 months	Application site: N/A Biopsy site: Lower abdomen	Skin collagen concentration was significantly increased compared with baseline ($+5.1\%$; $p < .01$)
Schmidt et al., 1994	0.3% estriol cream or 0.01% estradiol cream	18	6 months	Face	- Skin aging symptoms (vascularization, firmness, elasticity, moisture, wrinkle depth, and pore size) improved in both groups, but the effects of the topical estriol group were slightly superior to those of the estradiol group with regard to extent and onset
Creidi et al., 1994	1 g Premarin cream (0.625 mg conjugated estrogen/g of cream)	27	24 weeks	Face	- Skin thickness significantly increased in the treatment group compared with placebo ($p = .013$) - Fine wrinkles significantly improved in the treatment group compared with placebo ($p = .012$) - Improvement in roughness, laxity, and mottled pigmentation but did not reach statistical significance between the groups
Varila et al., 1995	2.5 mg of estradiol gel (Estrogel, same as 1.5 mg of 17B-oestradiol)	12	3 months	Lower abdomen	- Amount of skin collagen, as measured by skin hydroxyproline content, significantly increased during oestradiol treatment ($p = .012$) - Levels of carboxyterminal propeptide of human type 1 procollagen significantly increased after treatment - Levels of aminoterminal propeptide of human type III procollagen increased, but not statistically significant
Piérard-Franchim-ont et al., 1995	Cyclic transdermal hormone replacement therapy using estradiol 3.2 mg (Systen TTS, Cilag)	15	1 year	Lateral arm	- Water-holding capacitance of the stratum corneum was significantly increased in the treatment group, as measured with the plastic occlusion stress test
Callens, 1996	17B-etsradiol gel (Estrogel) or oestradiol transdermal system (Estraderm TTS)	49	58 months (range: 2-170 months)	Thigh, buttocks, abdomen, arm, inner forearm, outer forearm, or neck	- Skin thickness (measured with skin echography) and sebum (measured with Sebumeter) significantly increased in the treated group compared with the untreated one - Hydration (measured by capacitance) and microtopography (measured by image analysis) not significantly different between the treated and untreated groups
Schmidt et al., 1996	0.01% estradiol, 0.3% estriol cream	59	6 months	Face and neck	- Elasticity and firmness of the skin markedly improved and wrinkle depth and pore sizes decreased in both treatment groups - Type III collagen significantly increased in both treatment groups
Ashcroft et al., 1999	Evorel hormone replacement therapy patch, 25 ug estradiol/24 hr	9	80 days	Upper inner arm	Increased wound healing observed with decreased wound size, increased collagen levels, and increased fibronectin levels in the treatment group at the site of the wound
Sator et al., 2001	Transdermal estrogen (Estraderm TTS)	13	6 months	Temporal bone, inner upper arm, suprasternal region	- Skin surface lipids significantly increased when oral progesterone added to the regimen; but when only estrogen given, significant decrease in skin lipids - Epidermal hydration, skin elasticity, and skin thickness significantly increased in the treatment group compared with controls
Fuchs et al., 2003	0.01% estradiol cream	44	6 months	Face (temple hairline)	- Epidermal thickness significantly increased by 23% compared with controls - Markers of skin aging (rete peg pattern, epidermal thickness) significantly improved/reversed
Son et al., 2005	0.01% 17B-estradiol	13	2 weeks	Buttock	- Expression of type 1 procollagen, tropoelastin, fibrillin-1 mRNAs increased - MMP-1 protein levels reduced

Table 1 (continued)

Study group	Treatment group (n)	N	Treatment length	Treatment Location	Outcome of interest
Patriarca et al., 2007	0.01% micronized 17B-estradiol gel	15	16 weeks	Face	- Keratinocyte proliferation and epidermal thickness increased - Epithelial and dermal thickness significantly increased compared with baseline - Amount of collagen significantly increased compared with baseline
Rittié et al., 2008	0.01%, 0.1%, 1%, or 2.5% estradiol	40	2 weeks	Sun-protected hip, photo-damaged forearm, face	- Collagen production (quantified by procollagen I and III mRNA and collagen 1 protein levels) stimulated in sun-protected hip skin but not in photo-aged forearm or face skin in postmenopausal women
Sumino et al., 2009	17-beta estradiol patch (Estraderm M)	19	12 months	Forearm	- Skin elasticity significantly increased from baseline to after treatment (64.1 to 67.4%; $p < .05$)
Moraes et al., 2009	0.01% 17-beta estradiol	18	24 weeks	Face	Statistically significant increase in epidermal thickness, number of dermal papillae, fibroblasts, and dermal vessels
Neder and Medeiros, 2012	0.05% estradiol cream	40	30 days	Pre-auricular region	Metalloproteinase-1 enzyme expression not significantly different in keratinocytes, fibroblasts, and endothelial cells before and after treatment
Patriarca et al., 2013	0.01% 17-beta estradiol gel	15	24 weeks	Face	Hyaluronic acid concentration significantly increased
Masuda et al., 2013	0.06% estradiol gel (l'estrogel)	79	8 + 16 weeks	Arms	Fineness of texture (measured by digital microscope) increased in application site (forearm) and cheek (unapplied site)
Silva et al., 2017	0.01% 17-beta estradiol	15	24 weeks	Face	Types I and III facial collagen significantly increased at the end of treatment

Sator et al., 2001; Schmidt et al., 1994, 1996; Silva et al., 2017; Son et al., 2005; Sumino et al., 2009; Varila et al., 1995) or topical isoflavone (Table 2; Bayerl and Keil, 2002; Moraes et al., 2009; Patriarca et al., 2013; Silva et al., 2017) product on the skin of menopausal or post-menopausal women were included. The area of the skin receiving the topical treatment varied among the studies, including the face, abdomen, buttocks, forearms, and thighs.

Sample size ranged from 8 to 234 participants, and the length of treatment varied between 2 weeks and 58 months. Various outcomes of interest were evaluated in the studies, such as skin elasticity, epidermal thickness, hyaluronic acid concentration, collagen concentration, facial wrinkles, fineness of texture, elasticity, wound healing, sebum production, and skin hydration.

Topical estrogen products

Our literature review revealed 23 studies evaluating the effect of topical estrogen on postmenopausal skin (Table 1). The studies differed in various ways, such as in study design, method of application of topical product, concentration of topical estrogen product, concomitant administration of systemic therapy, and presence of a control group. For instance, some studies were structured as a case series that analyzed the effect of topical estrogen on the skin at baseline and again at the end of treatment in the same patient. Other studies were structured as a case control with one group of patients receiving the topical estrogen product and another group receiving placebo or nothing at all. Yet others utilized internal controls, where one part of the patient's body received the topical estrogen product and the contralateral side received either nothing or placebo. The method of topical application of the estrogen product also varied among studies, including gel, ointment, patch, or cream. The dose and concentration administered varied as well. Of note, the site most commonly treated in the studies was the face (n = 12), followed by the arms (n = 8), abdomen (n = 5), buttocks (n = 2), and hips (n = 1).

Adverse effects were rarely reported among the studies, and if so, were very mild. For instance, a study utilizing a transdermal estrogen patch reported temporary breast tenderness in three patients and one case of local reddening at the application site of the hormone patches (Sator et al., 2001). Most studies reported no systemic symptoms attributable to the estrogens, including vaginal bleeding, vasomotor symptoms, or edema (Jemec and Serup, 1989). Several studies tracked serum follicle-stimulating hormone, prolactin, and estradiol levels before and after treatment to determine whether local application could exert systemic effects, and all reported no significant changes in these parameters.

Interestingly, one study reported that local application of estradiol gel on the forearm led to an improvement in the fineness of the texture on the application site; however, the skin on the cheek, which was a distant site from where the gel was applied, also had similar improvement, suggesting the possibility of a systemic effect (Masuda et al., 2013). Lastly, some study protocols entailed the concomitant administration of oral progesterone to prevent endometrial hyperplasia (Bolognia et al., 1989; Brincat et al., 1987, 1987; Castelo-Branco et al., 1992; Sumino et al., 2009), but others did not (Varila et al., 1995). Further details about the studies can be seen in Table 1.

Table 2
Studies evaluating the effect of topical isoflavone on the skin in postmenopausal women

Study group	Treatment group (n)	N	Treatment length	Treatment Location	Outcome
Bayerl and Keil, 2002	Creams that contain phytoestrogens (0.0075% or 0.015% isoflavone)	234	12 weeks	Neck, face, upper arm	- Improved skin dryness* and roughness* - Reduction in facial wrinkles* and skin looseness*
Moraes et al., 2009	Gel with isoflavones (genistein 4%)	18	24 weeks	Face	Increase in epidermal thickness* and number of vessels*, fibroblasts, and dermal papillae
Patriarca et al., 2013	4% genistein gel	15	24 weeks	Face	Increase in hyaluronic acid concentration*
Silva et al., 2017	4% genistein gel	15	24 weeks	Face	Increase in types I and III collagen production*

* Statistical significance of at least $p < .05$.

Topical isoflavone products

Preliminary studies about isoflavones in skin have also been performed (Kaari et al., 2006; Kotsopoulos et al., 2000; Polito et al., 2012); however, evidence in support of the efficacy of isoflavones (especially topical formulation on postmenopausal skin) remains scarce. Our literature review identified four studies that evaluated the effect of topical isoflavones on postmenopausal skin (Table 2). The first was a controlled open European multicenter study that examined the effects of a cosmetic cream preparation including isoflavone (Novadiol) in 234 postmentopausal women (Bayerl and Keil, 2002). Throughout the 12-week treatment period, subjects applied isoflavone cream (concentration of 0.0075% in the morning and 0.015% in the evening) on the face, neck, and one upper arm, with the other arm serving as an untreated control. Upon evaluation, skin dryness and roughness were significantly improved in the treated areas by 32.9% and 22%, respectively, compared with the untreated skin. Additionally, facial wrinkles and skin looseness were significantly reduced by 22% and 24%, respectively. However whether these changes were definitely due to the isoflavone or moisturizing vehicle is difficult to identify.

The subsequent three studies evaluated different parameters of the effect of an isoflavone gel containing 4% genistein on the facial skin of postmenopausal women (Moraes et al., 2009; Patriarca et al., 2013; Silva et al., 2017). Preauricular skin biopsies were performed before and after 24 weeks of topical application to quantify the results. In the first study, Moraes et al. (2009) studied skin morphologic parameters and observed a 20% increase in epidermal thickness and 77% increase in number of dermal vessels ($p < .05$). In contrast, the increase in both the number of dermal papillae and fibroblasts was not significant (Moreas et al., 2009). Subsequently, Patriarca et al. (2013) evaluated the skin's extracellular matrix before and after treatment, showing a significantly increased hyaluronic acid concentration when compared with baseline ($p < .05$). Lastly, Silva et al. (2017) quantified and compared facial collagen concentrations before and after treatment and found a significant increase in the amount of both type I and type III facial collagen after treatment completion (24 weeks; $p < .001$).

In these studies, no significant systemic effects were detected after topical use of the gel using hormonal vaginal cytology, transvaginal ultrasonography, and/or serum estradiol as markers (Moraes et al., 2009; Patriarca et al., 2013; Silva et al., 2017). Additionally, these three studies utilized an application of estradiol gel as the control group, which showed that when topical estrogen was compared with topical isoflavone, estrogen was superior and resulted in larger improvements in skin health over the treatment period ($p < .01$; Moraes et al., 2009; Patriarca et al., 2013; Silva et al., 2017).

Discussion

The postmenopausal period is characterized by a physiological cessation in ovarian production of estrogen (Greendale et al., 1999), which provokes significant changes in the characteristics of EDS (Thornton, 2013). Estrogen's key role in maintaining the skin's structural and functional integrity is well established with evidence that shows that estrogens are essential for skin hydration, sebum production, improved barrier function of the stratum corneum, and increased collagen and elastin content (Duarte et al., 2016; Verdier-Sévrain, 2007).

Numerous studies have also investigated the effects of estrogen replacement on EDS, many of which examined the systemic effects of estrogens administered orally or percutaneously (Masuda et al., 2013). Despite estrogen supplementation having a positive effect on the skin, the use of exogenous estrogens poses a risk for breast, ovarian, and endometrial cancers. Thus, an increasing number of studies have been performed to evaluate the efficacy of topical estrogens and estrogen receptor agonists. Although an absence of systemic effects after topical estrogen application has been described by many investigators (Moraes et al., 2009; Silva et al., 2017), some had contrasting results.

For instance, Masuda et al. (2013) described a decreased incidence of hot flashes in postmenopausal women after application of a gel formulation that contained 0.06% estradiol gel, suggesting that topical applications could indeed exhibit systemic effects via blood circulation in addition to exerting local action on the application site (Masuda et al., 2013). However, a Cochrane meta-analysis of 19 trials with 4162 women found that topical vaginal estrogen therapy was not associated with an increased risk of endometrial hyperplasia compared with placebo; thus, the addition of progesterone for uterine protection is not needed, even when estrogen is directly applied to the vagina and vulva (Suckling et al., 2006). In general, the systemic absorption of local or topical estrogen therapies is thought to be quite low and does not increase the risk of venous thromboembolic events, as seen with systemic estrogen therapies (Ballagh, 2005). Thus, whether the application of topical estrogens may potentially result in unwanted systemic effect is currently unclear, and topical estrogens are not widely used to treat EDS.

More recently, the feasibility of achieving the beneficial effects of estrogen with plant hormones (ie, isoflavones) has been examined. Soy isoflavones are a type of naturally occurring isoflavonoid produced almost exclusively by members of the Fabacea family, which includes soybeans, lentils, and red clover (Irrera et al., 2017). The most abundant isoflavone is genistein. Isoflavones display structural similarities to the 17-B estradiol hormone; they can interact with the estrogen receptor and are therefore classified as phytoestrogens in mammals, or dietary estrogens. Polito et al. (2012) suggested that isoflavones may have an efficacy comparable to estrogen replacement therapy with regard to reversing skin changes associated with menopause. Additionally, studies have shown that when topically applied, certain phytoestrogens behave like estrogens by causing a proliferation of the epidermis, supporting collagen synthesis and reducing enzymatic collagen degradation (Sator et al., 2004).

Isoflavones (namely genistein) are notable for their high affinity for ER-β, which is found more frequently in the skin, bones, and cardiovascular system (Cassidy et al., 2006), and a low affinity for ER-α, which is found in the uterus and breasts (Duarte et al., 2016). In fact, because of their ability to be tissue-selective, isoflavones are also considered selective estrogen receptor modulators, a classification to which tamoxifen and raloxifene belong (Messina, 2014). Although larger well-controlled studies are needed, isoflavones are potential candidates to treat EDS while avoiding the negative aspects of systemic estrogen. Local estrogens have a low systemic absorption and thus associated risks, but genistein would be expected to carry an even lesser risk due to the more limited receptor selectivity.

Although studies have shown the beneficial effects of both topical estrogens and isoflavones on skin aging, the biological potency of isoflavonoids is significantly inferior to that of synthetic estrogens (Markiewicz et al., 1993). In fact, the majority of studies found topical genistein to be inferior to topical estrogen, and this difference was significant ($p < .01$; Moraes et al., 2009; Patriarca et al., 2013). Additionally, one study assessed patient satisfaction after treatment (blinded) and showed that 88% of patients in the estrogen group observed improvements in their skin, which was significantly higher than 50% of patients who noticed an improvement in the isoflavone group ($p = .01$; Moraes et al., 2009).

Conclusions

The effects of estrogen deficiency on the skin are an important endogenous cause of aging skin in women. Treatment strategies that

target the underlying hormone deficiency and not the resulting symptoms are limited. Clinically, it is plausible that topical estrogen products can be used cosmetically to improve skin dryness, texture, and elasticity and reduce wrinkles in EDS. However, concerns exist with regard to the safety of topical estradiol, and there is limited data on the efficacy of isoflavones. Thus, more research is needed to support the use of topical agents to prevent and treat EDS.

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