PERIMENOPAUSAL INFLUENCE ON SKIN, HAIR AND APPENDAGES

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THE SKIN AS AN ENDOCRINE TARGET ORGAN

Numerous functions of the skin are subject to hormonal influences in all phases of life. In infancy, maternal androgens can cause steroid acne, and from puberty the increasing levels of adrenal androgens have an effect on the skin. With the right genetic predisposition, the sebaceous gland-stimulating effect of androgens [1] is a co-factor for the development of acne in adolescents. To a lesser degree, gestagens can also stimulate the activity of the sebaceous glands [2] – a condition that is clinically relevant due to possible acne flares during pregnancy, the common premenstrual exacerbation of acne, as well as the late manifestations of premenopausal acne.

In contrast to these stimulating effects on the sebaceous gland, the estrogens have an inhibiting effect [3]. A decrease in size of the sebaceous gland and sebum-inhibiting effects of estrogen administration led to the – meanwhile historical – treatment of acne with estrogens.

In animal trials, proliferation-promoting effects of estrogens on hair follicles were also observed, a condition that may indirectly explain postpartum hair loss. The hair follicles, which are subject to stronger estrogen influences during the last trimester, are synchronized in the anagen phase. The postpartum decrease in estrogen level once more leads to normal mosaic-like distribution of the hair growth cycles and thus to loss of the hairs that were previously in a prolonged growth phase. Although the growth-promoting effect of estrogens on the hair can be regarded as confirmed and has in practice led to the therapy of hormonal hair loss with hair tinctures containing estrogen, there are no extensive clinical studies that sufficiently document the therapy success of estrogens in hair loss.

Recently, the attention of dermatologists has been focused more strongly on the second major period of hormonal changes in the life of women: the climacterium and the menopause. The association with those signs of skin ageing that occur for the first time during this period is evident. Although ageing of the skin has complex, multifactorial causes, the effects of estrogens on the structures involved in ageing still provide an empirical indication of the causality of estrogen deficiencies in the ageing process of the skin.

SKIN AGEING: MORPHOLOGY, FUNCTION, INTERACTIONS WITH ESTROGENS

The first visible signs of skin ageing are often a slackening of the facial contour and the presence of small wrinkles,

which become noticeable around the age of 40 to 45. At the same age in life, women also observe increasing dryness of the skin, which can often cause itchiness.

These clinical signs of so-called "endogenous" skin ageing – genetically coded, but subject to endogenous, metabolic influences –, which also manifest themselves in skin areas that are protected from UV radiation by clothing, differ clearly from the symptoms of "exogenous" UV-mediated "photo-ageing". This is characterized by yellowish, elastically thickened skin with deep wrinkles, actinic keratoses and irregular pigmentation.

The histological status of older skin reflects the functional changes and correlates with the clinical aspects of the skin. The primary symptom is the reduced thickness in all three main layers of the skin (epidermis, dermis, subcutis). The cutaneous appendages (sebaceous glands, sweat glands, hair follicles) also show reduced size and the lumen of the skin vessels is reduced. This results in a reduction of the hydrolipid film that is responsible for the smoothness and moisture of the skin surface, and in thinning of the hair, which grows more slowly and with less density. The skin, which is now poorly vascularized, becomes pale.

Atypical mitoses occur in the basal layer of the epidermis, making the development of skin carcinomas possible. The natural moisturizing factor (NMF) localized in the epidermis – a mixture of amino acids, uric acid, sugar compounds and others – decreases quantitatively in accordance with the decrease in thickness of the epidermis, whereby the epidermal skin moisture level is reduced.

In the dermis, there are distinct changes to the collagen and elastic connecting tissue with an increase of type I collagen in the old skin, and fragmentation of the elastic fibers responsible for loss of skin elasticity and firmness.

The subcutaneous fatty tissue has mechanical and thermal protection properties as well as hormone metabolic properties. The conversion of androgens into estrogens induced by the enzyme localized in the fatty tissue, aromatase, makes a quantitatively relevant contribution towards the total estradiol level in the human, so that a significant reduction of the fatty tissue layer can contribute towards the decrease in estrogen level. Borders between estrogen deficiency symptoms in the skin and estrogen deficiency due to age-related fatty tissue atrophy are therefore fuzzy.

The estrogen stimulation ability of the skin has been documented by the detection of estrogen receptors in normal skin, in acne and in hirsutism [4, 5]. In immuno-histochemical studies, estrogen-binding sites were detectable in the basal keratinocytes, sebaceous glands and skin vessel endothelia, and in fibroblasts – structures that are involved in the ageing process [6]. Therefore, it may be assumed that the stimulating estrogen influences on the skin decrease with increasing estrogen deficiency.

Positive effects of estrogens on the dermal connecting tissue are known both for the basic substance, with an increase in acid mucopolysaccharides and hyaluronic acid and the consecutive increase in dermal water storage [7], and from the influence of estrogens on collagen connecting tissue and structural improvement of elastic fibers due to estrogen [8].

The experimentally confirmed effects are clinically relevant: in gynecology, an increase in the mitotic activity of vaginal cells in the therapy of vaginal

atrophy with estrogen ointments has long been exploited. The increase in epithelial proliferation rate and the dermal effects of the estrogens contribute towards an increase in the skin thickness of postmenopausal women with hormone replacement within 5 months of the beginning of therapy [9]. In contrast, an ovarectomy or the menopause leads to a significant reduction in skin thickness after only a few months [10].

Studies in primary fibroblast cultures of different age groups show linear regression of collagen-I and -III synthesis with increasing age, with a reduction by 29% in women over the age of 49 [11]. However, in a retrospective study significantly higher collagen-III levels were measurable in fibroblast cultures from women with long-term hormone replacement than in those of a control group without hormone replacement. Only six months after hormone replacement, significant increases in collagen-III were however detectable.

Whilst the beneficial effects of systemic hormone replacement on individual skin parameters were initially documented histologically or in cell cultures, more recent studies demonstrate the positive effects of hormone replacement therapy (HRT) on maintenance of the physiological skin function and protraction of the signs of aging in the skin. Especially the reduction of elasticity of the skin, which progresses at a rate of about 1.5% per year as of the menopause [13], is limited by systemic hormone replacement. Studies of age-associated rheological properties of the skin in different age groups have shown that women with HRT have a considerably lower loss of elasticity of the skin than women without hormone replacement [14]. The reports of other authors also show clearly that systemic hormone therapy has a positive effect on an important symptom of ageing skin, namely elasticity, whilst other properties such as depth of wrinkles or moisture of the skin are not improved objectively [15]. The increase in skin thickness that can be measured by ultrasound [15, 16] reflects the increase in rate of collagen-I and III synthesis in systemic hormone replacement [16].

Local Estrogen Therapy

Until recently, local therapy of the skin with hormones was not an issue of particular interest. Especially the risk of possible systemic hormonal side effects, but also the small number of studies of estrogen effects in the skin are possible explanations for the lack of extensive dermatological studies to date. Possible substances are estradiol and estriol. The latter has a marked epidermotropic effect [17] and no systemic hormonal effects on the endometrium [18].

In a pilot study, significant improvements in skin moisture, firmness and elasticity of the skin, and skin vascularization were observed after a treatment period of 6 months in 17 menopausal women who treated the facial skin with 0.1% estriol ointment daily. The depth of wrinkles also decreased significantly in 56% of the women, and pore size was also decreased. The effects of treatment occurred after 2.7–3.8 months in 16/17 patients. The hormone parameters, which were determined at monthly intervals, showed a significant prolactin reduction [19].

In a further study, two groups of postmenopausal women without hormone replacement were treated with 0.01% estradiol ointment (n = 10) or with 0.3% estriol ointment (n = 8). Gynecological examinations were per-

Figure 1a. Wrinkles before therapy with 0.3% estriol ointment.

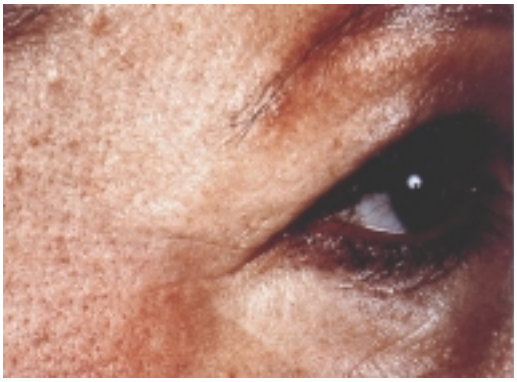

Figure 1b. Wrinkles after therapy with 0.3% estriol ointment.

formed prior to commencement of the therapy, after 3 and 6 months. Clinically, the depth of wrinkles, firmness and elasticity of the skin, skin moisture and pore size were documented. The clinical findings were objectivated by measurement of wrinkle depth using profilometry and measurement of skin moisture using corneometry. Clinically, the 0.3% estriol ointment was slightly superior to the 0.01% estradiol ointment with regard to depth of wrinkles and pore size (Fig. 1 a, b). In all patients in both groups, vascularization, skin moisture and elasticity had improved at the end of treatment. In both groups, there were significant reductions in the depth of wrinkles (Table 1). The hormone levels for E2, FSH and PRL showed no significant differences between the baseline values and the final values in the group treated with estradiol ointment. Also the KPI index did not show any change in both groups [19]. With regard to side effects, hyperpigmentation of the cheeks was observed in one patient each in both groups [20].

In a follow-up study, immuno-histochemical studies of the collagen-I/collagen-III fraction were performed. These showed significant increases in collagen-III at the end of therapy (Fig. 2 a, b). The other positive results were

Table 1. Clinical effects of treatment with estradiol ointment vs. estriol ointment on symptoms of ageing skin in 58 patients

	Estradiol 0.01% (n = 30)		Estriol 0.3% (n = 28)	
	Improvement in % patients	Weeks until initial manifestation	Improvement in % patients	Weeks until initial manifestation
Vascularization	100	9	96	7
Firmness and elasticity	100	13	96	11
Moisture	100	9	96	8
Depth of wrinkles	87	16	89	17
Pore size	73	19	61	16

confirmed with a larger patient population (30 vs. 30). However, in both groups the hormone analyses showed significant increases in prolactin.

In order to exclude systemic hormonal side effects, it is therefore absolutely necessary to limit the application area and the dose of ointment applied daily. The effects of estrogen ointment on ageing processes in menopausal women were also confirmed for conjugated estrogens in a randomized, double-blind study [21]. Significant improvements in the wrinkles and an increase in dermal and epidermal skin thickness characterized the Premarin group.

These first study results with local hormone therapy for ageing skin showed good results with minimal side effects. Nonetheless, concentrations or application surfaces with which local estrogen ointment therapy can be carried out without the risk of hormone effects due to systemic absorption are by no means confirmed. These issues should be investigated in further studies.

Discussion

In addition to the new positive aspects of multiple estrogen effects that expand the therapeutic range of hormone replacement therapy, the role of gestagens on the skin of the menopausal woman, which are only known in some aspects so far, must also be inves-

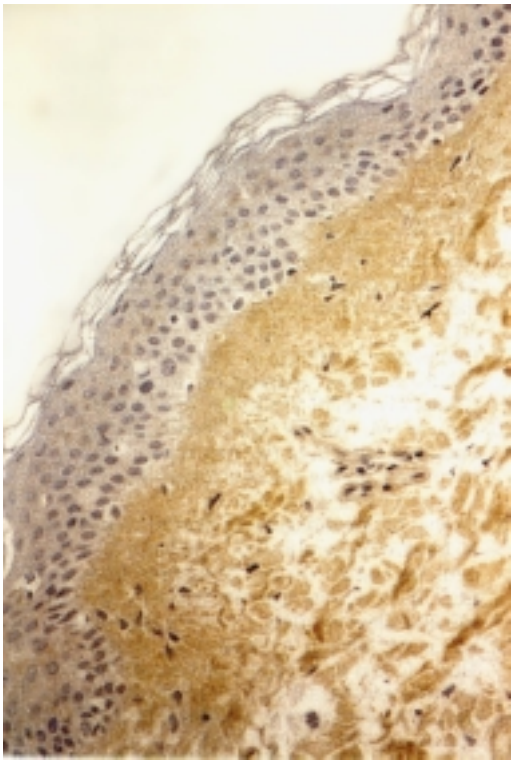

Figure 2a. Collagen-III before therapy with topical estriol.

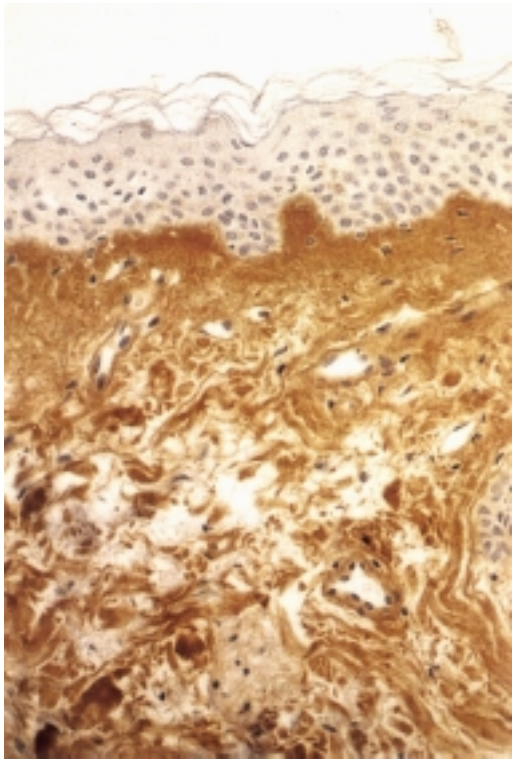

Figure 2b. Increase in collagen-III after therapy with topical estriol.

tigated. From studies with sebaceous glands and hair follicles, we know that the gestagen effects on these structures are diametrically opposed to those of estrogen. In genetically predisposed women, the promotion of sebaceous gland activity and partial androgen effects on the hair follicle, which can cause hair loss, may be an explanation for the acne eruptions common in the perimenopausal phase, or for the supposed "climacteric" hair loss. Thus, additive gestagen administration in HRT is the "dark side" of hormone replacement therapy for dermatology. Studies have shown that postmenopausal women receiving estrogen/gestagen therapy have significantly higher sebum levels than women receiving only estrogen replacement [15]. Own studies have confirmed these results [22]. These findings are relevant mainly in women with an acne predisposition, or in women with a history of androgenic hair loss. In such cases, an anti-androgen such as cyproterone acetate should be used as the gestagen component in HRT.

The impact of a deficiency of other hormones or growth factors such as somatotropin, IgF-1, epidermal growth factor or fibroblast growth factors on skin ageing are worth discussing although results have remained rather poor, to date [23].

Ageing skin in the perimenopausal phase presents itself as a consequence of complex processes, among which the hormone deficiencies certainly play a role to which not enough attention has been paid so far. With estrogen replacement therapy, it is possible to substitute a partial aspect of ageing skin – the estrogen deficiency. However, the gestagen component of HRT deserves attention as a possible co-causality for chronic hair loss and rare cases of late acne. One possible therapy for ageing skin in future will lie in the administration of estrogen ointments with a suitable concentration. Thus, local hormone replacement of the skin, which must be regarded as estrogen-deficient, can be achieved.

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