Skin treatments and dermatological procedures to promote youthful skin

Paul G Sator

Department of Dermatology, Municipal Hospital Lainz, Vienna, Austria

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Abstract: The skin, the largest organ of the body, is the organ in which changes associated with aging are most visible. With increasing frequency, patients are requesting information and treatments that improve the appearance of their skin. Corresponding to this trend, there is an increasing number of products and methods available that claim to aid this pursuit. First, a change of the patient's lifestyle (eg, sun behavior, nicotine abuse, and nutrition) must take place. Only then may other methods be used. This article reflects on the following topics: topical retinoids, peels, botulinum neurotoxin, soft tissue fillers, lasers, topical and systemic endocrinological therapies, and phytohormones. A thorough knowledge of the properties (benefits, limitations, and complications) of the expanding array of possibilities for rejuvenation of the skin is essential for any physician treating patients with cosmetic complaints.

Keywords: skin aging, topical retinoids, peels, botulinum neurotoxin, soft tissue fillers, lasers, topical endocrinological therapies, systemic endocrinological therapies, phytohormones

Introduction

The skin is one of the largest organs of the body and, like all other tissues, it undergoes degenerative processes during aging. The skin represents the major organ in which aging-related changes are visible (Zouboulis and Boschnakow 2001). Skin aging is associated with increased rates of skin diseases including skin tumors, and with concomitant psychological distress caused by the deterioration in appearance. Although the main focus of public medicine has long been on age-related chronic diseases of other systems, such as arthritis, heart disease, and cancer (Kligman and Koblenzer 1997), skin aging and its diseases have become increasingly important. Most women in developed societies can expect to spend one-third or more of their lifetime in the postmenopausal period (Kligman and Koblenzer 1997) when the external signs of aging are of utmost importance for most.

Skin aging is caused by a combination of factors including genetic disposition and endocrinological background as well as UV light, life habits (nutrition, nicotine, alcohol, and drugs), catabolic (infections and tumors), and further environmental factors. Many women notice a sudden onset of signs and symptoms of skin aging during menopause, such as a rise in skin dryness, loss of firmness, decrease in elasticity, and increase in skin looseness. There is a connection between these clinical signs and such phenomena as decrease in collagen and elastin, changes in basic substance, the ratio of type I/type III collagen, and alterations in vascularization (Brincat 2000). The external signs of skin aging are reflected in the histopathologic findings of the skin (Broniarczyk-Dyla and Joss-Wichman 2001).

Dermatology patients are requesting information and treatments to improve the appearance of their skin with increasing frequency. The number of products and methods claiming to aid in this pursuit are rising. Many different ways may be helpful. Patients look for a prompt improvement while physicians emphasize safety and efficacy.

Correspondence: Paul G Sator
Department of Dermatology, Municipal Hospital Lainz, Wolkersbergenstraße 1, A-1130 Vienna, Austria
Tel +43 1 80110 2422
Fax +43 1 80110 2633
Email paul.sator@wienkav.at

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General procedures

Sun protection

Sun protection is essential for every age and is a necessary addition to all other interventions against skin aging. Chronic low-dose irradiation by the sun causes wrinkles (Kambayashi et al 2001; Gordon 2005). Ultraviolet irradiation reduces production of type I procollagen, the major structural protein in human skin (Quan et al 2004). To avoid photoaging, it is essential to use sunscreens every day and to protect one's skin against UV A and B rays (a sun protection factor 15 is adequate, but a higher one is better). In addition, it is also important to use protective clothing or hats and to avoid the sun wherever possible.

Skin care

Cleansing and moisturizing the skin is important for many people. Properly cleaned and moisturized skin feels good to most people and looks better than dry skin. Effective products are available from most cosmetic companies and prevent irritant skin reactions and improve barrier functions. Sun protection, avoidance of cigarette smoke, and balanced nutrition is essential for the prevention of skin aging.

Topical retinoids

The topical retinoids, tretinoin and tazarotene, improve mottled hyperpigmentation, fine wrinkles, roughness, and lentigines (Kligman et al 1986; Kang et al 2001; Weiss 2005). One problem is skin irritation. To minimize this problem, it is useful to start with a relatively mild concentration of topical retinoids. If this is not enough, patients should reduce the application frequency. The aim must be to use the highest concentration that can be tolerated without significant irritation of the skin.

Peels

There are three categories of peels: deep peels (eg, phenol peel), medium peels (eg, 30% trichloracetic acid peel), and superficial peels (eg, alpha hydroxyl and salicylic acid peel). Creams with alpha hydroxyl and salicylic acid are also available for the everyday use of the patient. Depending on the depth of the peel, peels remove the uppermost layers of the skin.

Botulinum neurotoxin

Botulinum neurotoxin is a paralysing substance. It is used for softening glabellar frown lines, horizontal forehead lines, crow's feet, perioral smile lines, platysmal bands of the neck, and to elevate the eyebrows and lateral corners of the mouth (Gordon 2005).

A careful history should be taken to avoid complicating neurologic problems or the ingestion of medications that may interfere with the toxin. The toxin diffuses about 1 cm–1.5 cm from the injection site. This must be considered to avoid eyelid ptosis, for example. The patient should not manipulate the treated area after treatment to avoid unintended diffusion of the toxin. The contraction of the treated muscles after treatment may increase toxin uptake and increase the effectiveness of treatment. The effect of the toxin is seen after about a week.

Soft tissue fillers

Physicians have been searching for the ideal filler for more than a century. The use of injected paraffin for cosmetic purposes more than 100 years ago resulted in paraffinomas (Murray et al 2005). Many substances are available today.

Collagens

Collagen is a fibrous, extracellular, insoluble protein comprising a major component of connective tissues. Injectable collagen consists of varying concentrations of highly purifed bovine or human collagen. Sensitivity reactions and granulomatous responses have occurred in 1%–3% and 0.5% of patients, respectively (Cooperman et al 1985). Minor side effects such as bruising, redness, and swelling are seen after injection, but tend to resolve after a few days. Reimplantation is usually required in 3–6 months.

Bovine collagen

Bovine collagen is available in several formulations for fine lines as well as for deeper lines and folds. Patients must be allergy tested because of the possibility of rare allergic reactions. Two tests must be performed 3 weeks apart and treatment cannot be started until 3–4 weeks after the second allergy test.

Human-based collagen

No allergy testing is required.

Hyaluronic acid

Hyaluronic acid is a component of all connective tissues and is abundant in the human dermis. It is a naturally occurring glycosaminoglycan biopolymer, which provides a fluid matrix or lattice on which collagen and elastic fibers may develop. Its hydrophilic nature attracts and retains water

(Pollack 1999). The incidence of allergic reactions is so low that no allergy testing is required. Corrections with hyaluronic acid generally last longer than with collagen.

There are also several formulations for fine to deep lines. There are products that are manufactured through bacterial fermentation and there are others that are extracted from rooster combs. Patients using the latter must not have an allergy to avian products.

Unusual hypersensitivity and granulomatous foreign body reactions have been reported, but hyaluronic acids are generally safe and practical and need no allergy testing (Murray et al 2005).

Autologous fat

Neuber introduced the use of autologous fat for tissue augmentation in 1893 (Neuber 1893). Over the years, the popularity of Neuber's method has grown, but there is still no evidence-based gold standard method around. The longest lasting results are seen when used for atrophic skin conditions. Adverse events, such as fat necrosis, are temporary but not uncommon.

Allogenic products

Allogenic material is either obtained from cadaveric dermis or fascia, or engineered by methods using human cell lines and has a high biocompatibility with low antigenicity. These products are similar to the bovine collagens in indication and technique, but do not require allergy tests and have a shorter longevity.

Synthetic products

The production of synthetic products is cheaper and they are semipermanent or permanent implants. One of the first synthetic fillers was silicone. Today there are several substances available such as polylactic acid, polyalkylamide, polyacrylamide, and polytetrafluoroethylene. Adverse reactions with these agents can be serious.

Lasers

Laser is the acronym for "light amplification by the stimulated emission of radiation". Schawlow and Townes developed the first laser in 1958 (DiBernardo and Cacciarelli 2005). Lasers use light at various frequencies to attain a specific clinical result. They can be categorized by the medium in which the light energy is produced. Mechanisms of action include selective thermolysis and specific cell stimulation while leaving normal tissue unaffected. The immune system clears the unwanted material. Lasers can be used to cut, destroy, cauterize, and vaporize tissue. Dermatological indications are skin rejuvenation, tattoo removal, hair removal, and improvement in various skin abnormalities. For example, an ablative laser such as CO_2 or erbium would be considered for skin rejuvenation. Complications could be pigment changes, superficial skin changes, scarring, infection, bleeding, and accidential eye injury.

Surgical procedures

There are many methods of cosmetic surgery such as facelifts not covered by this article. Space limitations preclude an extensive discussion of this field.

Endocrinological therapies for skin aging

Skin is a target organ for various hormones (Zouboulis 2000). Sex steroids have a profound influence on both skin development and composition; adequate levels are required to facilitate its structural integrity and functional capacity (Raine-Fenning et al 2003). Hormonal action requires the binding of the hormone to specific receptors (Zouboulis 2000). Estrogen and other hormone receptors have been detected, inter alia, in keratinocytes, fibroblasts, sebaceous glands, hair follicles, endocrine glands, and blood vessels (Schmidt et al 1990). The receptors vary in density according to site, with higher concentrations of estrogen receptors in facial skin than in the skin at the pelvis or breast. Decreased sex hormones thus induce a reduction of those skin functions that are under hormonal control.

In clinical terms, many females experience a sudden onset of skin aging symptoms several months after menopause. One of the first signs which women experience is increasing skin dryness followed by a loss of skin firmness and elasticity. The increasing looseness of the skin at that stage outweighs other symptoms such as wrinkles. These symptoms correspond to changes in collagenous and elastic fibers that have been reported to be due to estrogen deficiency (Schmidt et al 1994). A significant decrease in skin collagen starting at menopause has previously been demonstrated (Castelo-Branco et al 1992). This negative effect of the menopausal years on the skin was first described by Albright in 1940, who noted that older women with osteoporotic fractures had a higher incidence of altered skin (Albright et al 1940). Among the various types of collagen, types I and III are of major relevance. Type I collagen

represents the predominant collagen type in adult human skin whereas type III collagen, also widely distributed throughout the body, predominates in fetal tissues. Both total collagen content and the ratio of type III to type I collagen decline with age (Sawas et al 1993). Skin collagen contents in adults decreases by 1% every year (Shuster et al 1985). This process is more evident in women than in men. Approximately 30% of skin collagen is lost in the first five years after menopause, with an average decline of 2.1% per postmenopausal year over a period of 20 years. Estrogens reverse this trend and increase skin collagen (Zouboulis 2000). Estrogens also enhance the synthesis of hyaluronic acid and promote water retention (Epstein and Munderloh 1975). Animal studies indicate that estrogens induce several changes in the connective tissue of the dermis, including increased mucopolysaccharide incorporation, hydroxyproline turnover, and alterations in the extracellular matrix (Holland et al 1994).

Epidermal cells – keratinocytes, Langerhans' cells, and melanocytes – are also target cells of steroid hormones (Zouboulis 2000). The estrogen receptor complex is able to support the expression of growth factors such as insulin-like growth factor type one (IGF-I), a mitosis-enhancing protein for keratinocytes (Tavakkol et al 1999). The Langerhans' cells are influenced by progesterone, with their number increasing during the luteal phase. Melanocytes are stimulated by 17β-estradiol (Gruber et al 2002).

Sex steroids are involved in many extragenital organ systems such as the urogenital tract, skin and hair, breast, and cardiovascular, nervous, or skeletal systems. Considering that most women spend one-third of their lives with estrogen deficiency, the potential field of action for hormone replacement therapy (HRT) is becoming increasingly larger.

Topical treatment

A placebo-controlled study examined the effect of a topically applied conjugated estrogen skin care cream (Premarin® 0.625 mg/g ointment) in 54 women (Creidi et al 1994). Evaluation criteria were profilometry and measurements of skin thickness by ultrasound. After a 24-week treatment period there was a significant increase in skin thickness in the Premarin® group as compared to the placebo group. Even in regard to small wrinkles, a significant reduction was observed in comparison to the placebo group after 12 and 24 weeks. No side effects were found.

A study was published on the action of topical 0.3% estriol and 0.01% 17β-estradiol in 59 patients (Schmidt et al 1996). The criteria evaluated by the authors were profilometry, corneometry, and clinical signs. Wrinkle depth was significantly reduced and skin hydration was improved. Apart from a rise in prolactin, no other systemic hormonal effects were detected. Histological tests of collagen parameters in 10 patients showed a significant increase in the collagen III fraction at the end of therapy after 24 weeks.

In a recent study, the effects of a 0.01% 17β-estradiol cream were compared with those of a 15% glycolic acid cream and a combination of both (Fuchs et al 2003). The effects examined in 65 patients after 6 months indicated an increase in epidermal thickness and were most marked in the combination group (38%), followed by the glycolic acid group (27%), and the 17β-estradiol group (23%).

Systemic hormone replacement therapy

A HRT consists of two components: estrogens and progestagens. Estrogens administered as monotherapy may result in undesired hyperplasia of the endometrium. To avoid this event, synthetic derivatives of progesterone and testosterone, known as progestagens, are combined with an estrogen compound and may be applied in a cyclical or continuous mode. An estrogen monotherapy is feasible in hysterectomized women, with a choice of oral, transdermal, and vaginal forms of application available.

Beneficial effects of HRT on the skin have been documented by several studies in respect of skin thickness as a mirror image of collagen content (Brincat et al 1987; Maheux et al 1994; Dunn et al 1997; Sator, Sator, et al 2001). A large retrospective multi-center study, NHANES I, conducted in 3825 women in the USA, showed that women under long-term substitution had one-third fewer wrinkles than non-substituted patients (Dunn et al 1997). Postmenopausal women with an HRT had significantly higher collagen content than untreated women (Brincat et al 1987).

One study examined the effects of three types of HRT in terms of skin aging in menopausal women (Sator, Schmidt, et al 2001): one group was given estrogen only via the transdermal route (Estraderm TTS® 50), the second group received estrogen by transdermal application in combination with vaginally applied progesterone (Estraderm TTS® 50 and 0.4 g progesterone vaginal suppository), and the third group was administered oral estrogen and vaginal progesterone (2 mg Progynova® and 0.4 g progesterone vaginal suppository). One group without treatment served as a control. Treatment was continued for 6 months. Skin surface lipids, epidermal skin hydration, skin elasticity, and skin thickness were measured at monthly intervals. Mean levels of epidermal skin hydration, elasticity, and skin

thickness were improved at the end of treatment based on both subjective and objective evaluation in patients with HRT. Skin surface lipids were increased during combined HRT, which may reflect stimulatory effects of the progestagen component on sebaceous gland activity, while estrogen alone has a sebum-suppressive action (Zouboulis 2001). A comparison of skin hydration and elasticity in UV-exposed and non-exposed areas revealed no significant difference. This finding suggests that both photoaged and UV-protected skin benefit equally from HRT. These results were confirmed by animal tests using the skin of rats (Tsukahara et al 2001).

Although the majority of publications consider the influence of HRT on skin aging to be positive, there are some authors who doubt or reject any effect of hormone replacement on skin thickness, collagen synthesis, or elastin (Oikarinen 2000).

Alternatives: phytohormones

The estrogen-like effects of some plants were first described in 1926 (Loewe et al 1927). Phytoestrogens are classified in three categories: isoflavones, coumestans, and lignans. The most thoroughly examined group of substances are isoflavones, which display some similarity to the mammal estrogen molecule and are found, inter alia, in soy, beans, lentils, and red clover. Flavonoids are also contained in wine, especially red wine. The most important isoflavones are genistein and daidecin. The group also includes the precursors formononetin (for daidecin) and biochanin (for genistein). Coumestans only occur in the sprouts of legumes. Lignans have no influence on estrogen receptors. The structural similarity to 17β-estradiol explains the estrogen-like effects, which may be traced back to the interaction of these substances with the estrogen receptor (Wang et al 1996). Nutrition in Asian countries, with its large phytoestrogen content, is thought to be the reason why Asian women rarely suffer from climacteric symptoms. The biological potency of isoflavonoids is significantly inferior to that of synthetic estrogens (Markieicz et al 1993). When phytoestrogens are topically applied, they behave like estrogens by causing a proliferation of the epidermis, supporting collagen synthesis and reducing enzymatic collagen degradation.

A controlled open European multicenter study examined the effect of a cosmetic cream preparation including isoflavone (Novadiol®) on 234 women: maximum age 65 years, at least 3 years since menopause, no HRT or other substances affecting the skin aging process (Bayerl and Keil 2002). The length of therapy was 12 weeks. The isoflavone cream was applied two times daily (in the morning with a concentration of 0.0075% isoflavone and in the evening with a concentration of 0.015% isoflavone) on the face, neck, and one upper arm. The other arm was untreated and served as a control. Skin dryness and roughness were significantly improved at the treated areas by 32.9% and 22%, respectively, in comparison with the untreated skin areas. Facial wrinkles were significantly reduced by 22% and skin looseness was significantly reduced by 24%.

Summary of hormonal therapies

Numerous publications on the effects of sex hormones on the aging process are available today. Without claiming that HRT can or should ever be regarded as an independent treatment of skin aging, these findings are still interesting to note, considering that they indicate a beneficial effect of HRT on the skin despite the fact that the results of the "WHI-Study" (Rossouw et al 2002) and the "Million Women Study" (Beral 2003) have shown negative effects of HRT on other organs. What is clear is that HRT must be rejected when it is solely considered for the prevention of skin aging. As an additional benefit in the treatment of menopausal conditions provided by a dermatologist with sufficient experience in the discipline of endocrinology, however, it is a very effective instrument to control intrinsic skin aging.

While the topical application of hormones is certainly a suitable alternative to a systemic HRT, it must be ensured that such a treatment is also administered by a dermatologist experienced in endocrinology given that concentrations and application areas need to be observed in order to avoid systemic side effects.

Phytoestrogens, topical and systemic, appear to be an effective method in the treatment of intrinsic skin aging. However, further data are still required, especially from controlled studies on long-term results of systemic application.

Conclusion

An increasing number of products and procedures exists to promote youthful skin. First, a change of the lifestyle (eg, sun behavior, nicotine abuse, nutrition) of the patient must take place. Only then can other methods be used. A thorough knowledge of the properties (benefits, limitations, and complications) of the ever-expanding array of possibilities for rejuvenation of the skin is essential for any physician treating patients with cosmetic complaints.

References

Albright F, Bloomberg E, Smith PH. 1940. Post-menopausal osteoporosis. *Trans Assoc Am Physicians*, 55:298–305.

Bayerl C, Keil D. 2002. Isoflavonoide in der Behandlung der Hautalterung postmenopausaler Frauen. *Akt Dermatol*, 28:14–18.

Beral V. 2003. Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet*, 362:419–27.

Brincat M, Versi E, Moniz CF. 1987. Skin collagen changes in postmenopausal women receiving two different regimen oestrogen therapy. *Obstet Gynecol*, 70:123–7.

Brincat MP. 2000. Hormone replacement therapy and the skin. *Maturitas*, 35:107–17.

Broniarczyk-Dyla G, Joss-Wichman E. 2001. Ageing of the skin during menopause. *J Eur Acad Dermatol Venereol*, 15:494–5.

Castelo-Branco C, Duran M, Gonzalez-Merlo J. 1992. Skin collagen changes related to age and hormone replacement therapy. *Maturitas*, 15:113–19.

Cooperman LS, Mackinnon V, Bechler G, et al. 1985. Injectable collagen: a six-year clinical investigation. *Aesthetic Plast Surg*, 9:145–51.

Creidi P, Faivre B, Agache P, et al. 1994. Effect of conjugated oestrogen (Premarin®) cream on ageing facial skin. A comparative study with a placebo cream. *Maturitas*, 19:211–23.

DiBernardo BE, Cacciarelli A. 2005. Cutaneous lasers. *Clin Plast Surg*, 32:141–50.

Dunn LB, Damesyn M, Moore AA, et al. 1997. Does estrogen prevent skin aging? Results from the first national health and nutrition examination survey (NHANES I). *Arch Dermatol*, 133:339–42.

Epstein EH, Munderloh NH. 1975. Isolation and characterization of CNBr peptides of human $[\alpha 1\ (III)]_3$ collagens. *J Biol Chem*, 250:9304–12.

Fuchs KO, Solis O, Tapawan R, et al. 2003. The effects of an estrogen and glycolic acid cream on the facial skin of postmenopausal women: a randomized histologic study. *Cutis*, 71:481–8.

Gordon ML. 2005. A conservative approach to the nonsurgical rejuvenation of the face. *Dermatol Clin*, 23:365–71.

Gruber CJ, Wieser F, Gruber IM, et al. 2002. Current concepts in aesthetic endocrinology. *Gynecol Endocrinol*, 16:431–41.

Holland EF, Studd JW, Mansell JP, et al. 1994. Changes in collagen composition and cross-links in bone and skin of osteoporotic postmenopausal women treated with percutaneous estradiol implants. *Obstet Gynecol*, 83:180–3.

Kambayashi H, Yamashita M, Odake Y, et al. 2001. Epidermal changes caused by chronic low-dose UV irradiation induce wrinkle formation in hairless mouse. *J Dermatol Sci*, 27:19–25.

Kang S, Leyden JJ, Lowe NJ, et al. 2001. Tazarotene cream for the treatment of facial photodamage: a multicenter, investigator-masked, randomised, vehicle-controlled parallel comparison of 0.01%, 0.025%, 0.05% and 0.1% tazarotene creams with 0.05% tretinoin emollient cream applied once daily for 24 weeks. *Arch Dermatol*, 137: 1597–604.

Kligman AM, Grove GL, Hirose R, et al. 1986. Topical tretinoin for photoaged skin. *J Am Acad Dermatol*, 15:836–59.

Kligman AM, Koblenzer C. 1997. Demographics and psychological implications for the aging population. *Dermatol Clin*, 15:549–53.

Loewe S, Lange F, Spohr E. 1927. Über weibliche Sexualhormone. *Biochem Zt*, 180:1–26.

Maheux R, Naud F, Rioux M, et al. 1994. A randomized, double-blind, placebo-controlled study on the effect of conjugated estrogens on skin thickness. *Am J Obstet Gynecol*, 170:642–9.

Markiewicz L, Garey J, Adlercreutz H, et al. 1993. In vitro bioassays of non-steroidal phytoestrogens. *J Steroid Biochem Mol Biol*, 45: 399–405.

Murray CA, Zloty D, Warshawski L. 2005. The evolution of soft tissue fillers in clinical practice. *Dermatol Clin*, 23:343–63.

Neuber F. 1893. Fettransplantation. *Chir Kongr Verhandl Dsch Gesellch Chir*, 22:66.

Oikarinen A. 2000. Systemic estrogens have no conclusive beneficial effect on human skin connective tissue. *Acta Obstet Gynaecol Scand*, 79: 250–4.

Pollack SV. 1999. Some new injectable dermal filler materials: hylaform, restylane, and Artecoll. *J Cutan Med Surg*, 3:24–7.

Quan T, He T, Kang S, et al. 2004. Solar ultraviolet irradiation reduces collagen in photoaged human skin by blocking transforming growth factor-beta type II receptor/Smad signaling. *Am J Pathol*, 165: 741–51.

Raine-Fenning NJ, Brincat MP, Muscat-Baron Y. 2003. Skin aging and menopause: implications for treatment. *Am J Clin Dermatol*, 4: 371–8.

Rossouw JE, Anderson Gl, Prentice RL, et al. 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women´s Health Initiative (WHI) randomized controlled trial. *JAMA*, 288:321–33.

Sator PG, Sator MO, Schmidt JB, et al. 2001. Messung der Hautdicke mittels Hochfrequenzultraschall zur Objektivierung einer Hormonersatztherapie in der Perimenopause. *Ultraschall Med*, 22:219–24.

Sator PG, Schmidt JB, Sator MO, et al. 2001. The influence of hormone replacement therapy on skin ageing. A pilot study. *Maturitas*, 39: 43–55.

Sawas M, Bishop J, Laurent G, et al. 1993. Type III collagen content in the skin of postmenopausal women receiving oestradiol and testosterone implants. *Br J Obstet Gynaecol*, 100:154–6.

Schmidt JB, Binder M, Demschik G, et al. 1996. Treatment of skin aging with topical estrogens. *Int J Dermatol*, 35:669–74.

Schmidt JB, Binder M, Macheiner W, et al. 1994. Treatment of skin ageing symptoms in perimenopausal females with estrogen compounds. A pilot study. *Maturitas*, 20:25–30.

Schmidt JB, Lindmaier A, Spona J. 1990. Hormone receptors in pubic skin of premenopausal and postmenopausal females. *Gynecol Obstet Invest*, 30:97–100.

Shuster S, Black M, McVitie E. 1985. The influence of age and sex on skin thickness, skin collagen and density. *Br J Dermatol*, 93:639–43.

Tavakkol A, Varani J, Elder JT, et al. 1999. Maintenance of human skin in organ culture: role for insulin-like growth factor-1 receptor and epidermal growth factor receptor. *Arch Dermatol Res*, 291:643–51.

Tsukahara K, Moriwaki S, Ohuchi A, et al. 2001. Ovariectomy accelerates photoaging of rat skin. *Photochem Photobiol*, 73:525–31.

Zouboulis CC. 2000. Human skin: an independent peripheral endocrine organ. *Horm Res*, 54:230–42.

Zouboulis CC, Boschnakow A. 2001. Chronological ageing and photoageing of the human sebaceous gland. *Clin Exp Dermatol*, 26:600–7.

Wang TT, Sathyamoorthy N, Phang JM. 1996. Molecular effects of genistein on estrogen receptor mediated pathways. *Carcinogenesis*, 17:271–5.

Weiss J. 2005. A review of clinical experience and recommendations for improving patient care. *Cutis*, 75:32–9.