EFFECTS OF HORMONE REPLACEMENT ON THE UROGENITAL TRACT

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INTRODUCTION

With a mean life expectancy of 75 to 80 years, women spend about 25–30 years of their life in the menopause, i. e. in a state of hormone deficiency. Within the scope of the menopause syndrome, signs of degeneration in the urinary and genital organs caused by estrogen deficiency play a decisive role and contribute significantly towards the loss of physical and psychosocial well-being [1]. The complaints in the region of the lower urinary tract occur within the first 5–10 years after the menopause, and are partly accepted with resignation. Often, however, they are also the reason for numerous unspecific visits to the doctor. In the USA alone, the costs of treating urogenital hormone deficiency symptoms are estimated at about 7 billion US dollars [2, 3].

AETIOLOGY

The mutual embryology of urethra and vagina (from the urogenital sinus and the Mueller's ducts), together with the hormone receptors known to be present in the urethra and the bladder neck, explain the hormone-dependent cyclical and trophic changes in the urogenital region that have an onset shortly after the menopause. The cause of all these objectively verifiable symptoms and the resulting complaints is, to a large extent, the decrease in estrogens in the tissue of the target organs and their receptors. This is associated with a reduction in blood circulation, tissue turgor due to loss of collagen, extracellular sodium and water retention, mitosis count, deposition of amino acids and total metabolism of the cells, as well as lipid and calcium metabolism with the relevant consequences for the vessels and bones.

A typical atrophy develops in the vagina, and the vaginal epithelium gets thinner. Genital discharge and subepithelial bleeding (senile colpitis), and often a ring-shaped constriction of the entire vaginal tube (vaginal kraurosis) are observed. Atrophic symptoms can also be found in the lower urinary tract. In the region of the urethra, the typical picture of urethral mucous prolapse can be found, a protrusion of the posterior urethral wall that is sometimes misinterpreted as a urethral polyp. Urethral stenoses are also found quite commonly, and together with atrophy of the bladder trigone and the remaining bladder epithelium, they frequently lead to the very fuzzy picture of an irritated bladder [4] or urethral syndrome [5]. Thereby, mainly pollakisuria and dysuria, and even insuppressible urge incontinence are reported.

In the postmenopause, there is an increased incidence of vaginal prolapse with cystoceles and even recto-

celes, together with sphincter failure, which in addition to the named pathogenetic factors is influenced by the frequency of childbirth, management of labour, heavy physical work and connective tissue weakness. However, estrogen deficiency would also appear to be one of the triggering factors for the incidence of manifestation in the postmenopause [6]. Apart from the described ageing processes, other possible triggering factors are medications (diuretics, alpha blockers), endocrinopathies (e.g. diabetes mellitus), central or peripheral neuropathies (multiple sclerosis, Parkinson's disease), overweight and smoking.

Diagnostics

Embryologically, the distal urethra must be regarded as a genital organ, and in addition to a histologically identical structure of multi-layered, non-keratinizing squamous epithelium it has the same hormonal dependence. Iosif et al [7], as well as Strittmatter et al [8] were able to verify the presence of estrogen receptors in addition to the progesterone and androgen receptors in the urethra. On average, proliferation is much higher in the vaginal epithelium than in the urethral epithelium, which is probably explained by the flushing and washout effects of micturition. In urethral and vaginal cytology, it is possible to identify those women whose endogenous estrogen production does not effect sufficient proliferation of the epithelium. The cytological control also allows us to control the therapy success and the compliance. Of course, this is much easier to achieve simply by measuring the pH with an appropriate test strip. A persistent alkaline pH during ongoing estrogen therapy is proof of non-compliance.

Therapy

The proof of steroid hormone receptors in the female urethra and the associated ability of tissue containing estrogen receptors to respond to estrogens is the real rationale for providing such hormone replacement. In addition to improving the degree of proliferation in the vagina and urethra, the blood flow in the peri-urethral venous plexus is increased, and the collagen content in the peri-urethral connective tissue is raised, thus improving elasticity. In individual studies, an alpha-sympathomimetic effect has been attributed to the estrogens [8–12]. Various hormone preparations are available for treatment of urogenital signs of ageing, some of which are being developed further. In addition to oral substitution with all combinations of estrogens and gestagens, parenteral deposit injections, percutaneous therapy with estradiol and gestagens, local treatment in form of creams, ointments, suppositories and – for long-term therapy – hormone-filled silicon rings are available. Numerous studies indicate that estrogen replacement has a therapeutic effect in postmenopausal women with various changes to the urinary tract [1, 13]. Despite the numerous publications on the use of hormone treatment for conservative therapy of female urinary incontinence, it must be noted that the results are discussed very controversially. On critical consideration of the available data, the curative effect of estrogen treatment cannot be regarded as proven. On the other hand, the so-called objective parameters are

only able to account for the morphological and functional changes due to hormone replacement to a limited degree. The intensity of the effect of estrogen replacement on the urethra, for example, depends on the receptor density and the binding affinity of the estrogen to the receptor. Estriol has a lower binding capacity on the estrogen receptor complex, and thus a shorter retention time in the cell nucleus. At low doses, estriol only demonstrates the early estrogen effects, e.g. epithelium proliferation in the vagina and urethra, but not the late estrogen effects such as proliferation in the endometrium. Epithelium proliferation leads to a marked improvement of subjective complaints, and presumably to a quantitative decrease in urinary leakage due to a "sealing effect", without any measurable effect on pressure. In order to achieve an influence on the urethral pressure components, a higher estradiol dose or the use of estrogens with greater receptor binding affinity (estradiol, conjugated estrogens), a longer duration of substitution, and possibly even adjuvant therapy measures such as pelvic floor training are probably necessary. The sparse objective results in literature currently do not permit us to make any statement concerning the extent to which estrogen treatment is able to reduce urinary incontinence, and especially stress incontinence, quantitatively. Van Geelen et al found a correlation between the urethral pressure profiles and 17β-estradiol serum concentrations [14]. Other studies report differing results for urodynamic parameters after estrogen treatment in postmenopausal women [15–18].

One of the most important applications, at least for local estrogen replacement, is in recurrent, uncomplicated infections of the urinary tract in postmenopausal women. If we assume that a physiological local flora in the vagina and acidity of the secretion provide a natural protection against the invasion of pathogens in the urinary tract, a reduction of pH and the production of physiological local flora would seem to be a clear therapeutic principle. Raz and Stamm [19] demonstrated the effect of such treatment very impressively.

Urge Symptoms

In agreement with the literature, our own results show that dysuria and urge symptoms respond particularly well to estrogens, whereby these symptoms with an incidence of up to 60% present a major problem for elderly women [20–22]. It has been shown that oral or vaginal estrogen therapy has a beneficial effect not only on urge symptoms, but also on sensory urge incontinence in 60–70% of cases. Motoric urge incontinence, on the other hand, is hardly improved by estrogens [23]. If various therapies are combined sensibly in urge continence (regular supply of fluid, bladder training, retention training and pharmacotherapy), an improvement and remission can be achieved in up to 80% of cases [214]. In our own patients, the local administration of estradiol resulted in complete remission after 12 weeks in 63% of patients, and to an improvement of urge symptoms in 18% of patients [22]. The extent to which the psychotropic effect of estrogens accounts for a marked improvement in urge symptoms, and improved self-esteem and a decrease in cohabitation problems eliminate the end organ bladder for somatization of psychosomatic problems cannot be shown with absolute certainty.

Administration

Orally administered estrogen increases the plasma estrone level, whereby estradiol is converted into estrone in the intestine [25]. Vaginal administration results in immediate absorption of estrone and estradiol, whereby studies have shown that the blood concentration after local estrogen administration is three times higher than after oral administration of an equivalent dose [26, 27]. Hilton et al found an increase in estradiol/estrone ratio after local vaginal administration. The authors conclude that these changes could be the reason for the alleviation of symptoms. However, it remains unclear whether an increase in estradiol/estrone ratio has an influence on the number and function of steroid hormone receptors [28]. A surprising fact is the good acceptance of vaginal estriol therapy in urogenital complaints. Almost all women regard vaginal treatment as pleasant and the majority of women prefer it to oral treatment. Especially when informing the patients, it must be made clear that local estrogen treatment will not take effect for three weeks [27]. Now local 17β-estradiol applications in the form of silicon rings or tablets to be inserted using disposable applicators show slight increases in serum levels in the first 36 to 48 hours only. After 2 days, postmenopausal serum levels were reached, and ultrasound scans also showed that the recommended doses had no effects on the endometrium. Therefore, these forms of administration must be regarded as absolutely safe and without risk with regard to the development of an endometrial or even breast cancer.

The additional use of alpha agonists would appear to support the effect of hormone treatment [21, 28]. This may be due to an increase in alpha-adrenoceptors as a result of estrogen therapy, with a corresponding improvement of urethral sphincter innervation.

In a study conducted by Cutner et al in patients with combined estrogen and high-dose progesterone therapy, a significant increase in irritable bladder symptoms (pollakisuria) and bladder filling pressures was observed during the progesterone administration phase [29]. Prior to planned surgery, local estrogen administration for a period of about 6–8 weeks has proved to improve the tissue status markedly, and to optimize the anatomical picture intraoperatively. In extreme atrophy, the improvement in local tissue status should therefore be used in addition to the mentioned positive effects in order to optimize operability.

Summary and Outlook

Beneficial effects of hormonal treatment in the postmenopause on the skeleton and the cardiovascular system are regarded as confirmed. By contrast, there are only very few studies that provide objective data on the changes of the lower urinary tract, and in particular the action mechanism of estrogens on the cellular level is still unclear and requires further investigation [30]. Estrogens have an influence on many aspects of the quality of life, and it is conceivable that urinary incontinence could be improved as a result of estrogen effects on other organ systems. The studies published so far, which contain mainly clinical and subjective data, show a beneficial effect of estrogen treatment on all urogenital atrophy symptoms, stress and urge in-

continence, as well as urge symptoms. If a patient refuses systemic therapy or if such therapy is contraindicated, the intravaginal administration of estrogens is a safe form of therapy with high acceptance.

In addition to the ointments, creams and suppositories already available, silicon rings are also available that allow continuous long-term treatment with estradiol for three months, have a high acceptance and avoid dosage or administration mistakes. In case of very severe or recurrent symptoms, the combination of oral and local hormone replacement makes sense and is successful. Adjuvant therapy measures such as drinking and micturition training, pelvic floor training, bladder-relaxing drugs, and even pessaries can make a major contribution towards the success of therapy. The therapy may be either cyclical or continuous, but it should always be a long-term treatment.

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