Hormonal influences on the female lower urinay tract

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The female lower urinary and genital tracts both arise from the primitive urogenital sinus and develop in close anatomical proximity from as early as the fourth week of embryological life. Oestrogen receptors are found in the vagina, bladder, urethra and muscles of the pelvic floor (Iosif et al 1981; Blackeman et al 1996). Six hormones have a significant influence on the female lower urinary tract with fluctuations in their level leading to macroscopic, histological and symptomatic changes. It is therefore not surprising that urinary symptoms may develop during the menstrual cycle, pregnancy and following the menopause. Oestrogen deficiency, particularly when prolonged, is associated with a wide range of urogenital complaints including frequency, nocturia, incontinence, urinary tract infections and the "urge syndrome." These may co-exist with vaginal symptoms of dryness, itching, burning and dyspareunia. In a study of 2045 British women aged between 55-85 years Barlow et al (1997) showed that urogenital symptoms had affected 48.5% of women at some time but only 11% were currently affected by individual symptoms.

Hormones and incontinence

The oestrogen sensitive tissues of the bladder, urethra and pelvic floor all play an important role in the continence mechanism. Oestrogens increase cell cycle activity and the "maturation index" of the urethral squamous epithelium (Smith 1976 and Blakeman et al 1996). Urethral closure pressure may also be increased by improved blood flow (Versi and Cordozo, 1986) in the submucosal vessels and sensitization of the alpha-receptors in urethral smooth muscle. (Screiter et al, 1976). Connective tissue metabolism is stimulated by oestrogens, increasing the production of collagen in periurethral tissues and therefore possibly reversing the changes which occur as a result of ageing. (Jackson et al 1996). The sensory threshold of the bladder may also be raised (Fantl et al 1988). The oestrogen status of the woman can therefore have a significant effect and this may be particularly important when there is already a degree of impairment.

Progesterone receptors are expressed inconsistently in the lower urinary tract and may be dependent on the oestrogen status of the woman. (Blakeman et al 1996). Progesterone has beta-adrenergic and anticholinergic properties and may therefore cause smooth muscle relaxation. Its effects have been studied most extensively in pregnancy where it is thought to account in part for the physiological hydroureter. (Van Wagenen & Jenkins 1939). During the normal menstrual cycle symptoms of urinary frequency and urgency occur most commonly in the luteal phase when progesterone levels are at their highest. A similar pattern may also be found in postmenopausal women taking Hormone Replacement Therapy (HRT). Burton et al (1992) found that women taking continuous oestrogen and cyclical progesterone for premature ovarian failure had an increase in urinary urgency during the progestogenic phase. In addition,

women with genuine stress incontinence on HRT may have an increase in their urine loss in the second half of their cycle. (Benness et al 1991). It would therefore appear that progesterone offsets the beneficial effects of oestrogen on the lower urinary tract. Androgen receptors are found in both the female blader and urethra but their role is at present unclear. (Blakeman et al 1997).

The prevalence of postmenopausal incontinence in the community is thought to be between 16-29% (Barlow et al, 1997; Thomas et al 1980, Jolleys 1988). While the ageing process is clearly a significant aetiological factor in the pathogenesis of urinary incontinence, there is conflicting evidence as to whether the menopause and oestrogen deficiency are independently important. Jolleys (1988) surveyed 937 women registered with a rural general practice and found the prevalence of incontinence was most common the the 45-55 year age group: a period which includes the menopause in most cases. Hiltin (1981) found a similar pattern in hospital practice, with 40% of women referred to a urogynaecology unit aged between 40-60 years with a mean comparable to the average age of the menopause. Iosif and Bekassy (1984) also reported that 70% of incontinent postmenopausal women related the onset of their urinary leakage to their final menstrual period. Most studies however show that many women develop incontinence at least 10 years before the menopause with Jolleys (1988) finding that significantly more premenopausal women were affected than postmenopausal women.

Salmon et al (1941) was the first to report the successful use of oestrogens to treat urinary incontinence over 50 years ago. Intramuscular oestrogen therapy was administered to 16 women with dysuria, frequency, urgency and incontinence for 4 weeks. Symptomatic improvement occurred in12 women until treatment was discontinued, at which time the symptoms recurred. Unfortunately this and other studies took place before the widespread introduction of urodynamic investigation and therefore almost certainly included a heterogeneous group of individuals with a number of different pathologies. Many studies were also observational, not randomised, blinded or controlled with a lack of outcome measures limiting their interpretation. The situation is further complicated by the fact that a number of different types of oestrogen have been used with varying doses, routes of administration and durations of treatment

Two meta-analyses have helped to clarify the situation. In the first, a report by the Hormones and Urogenital Therapy (HUT) committee, (Fantl etal, 1994), the use of oestrogens to treat all causes of incontinence in postmenopausal women was examined. Of 166 articles identified which were published in English between 1969-1992, only 6 were controlled trials and 17 uncontrolled series. The results showed that there was a significant subjective improvement for all patients and those with genuine stress incontinence. However, assessment of the objective parameters revealed that there was no change in the volume of urine lost. Maximum urethral closure pressure did increase significantly, but this result was influenced by only one study showing a large effect. In the second meta-analysis, Sultana and walters (1990) reviewed 8 controlled trials and 14 prospective uncontrolled trials and included all types of oestrogen treatment. They also found that oestrogen therapy did not produce a significant improvement in stress incontinence but may be useful for the often associated symptoms of urgency and frequency.

Although oestrogen given alone does not appear to be an effective treatment for stress incontinence, several studies have shown that it may have a role in combination with other therapies. Hilton et al (1990) used oestrogen (vaginal or oral) alone or in combination with phenylpropanolamine to treat 60 postmenopausal women with genuine stress incontinence in a double blind, placebo controlled study. Subjectively the symptom of stress incontinence improved in all groups but objectively only in the women given combination therapy. This type of treatment may be particularly useful for women with mild stress incontinence or those not suitable for surgery.

The prevalence of urge incontinence increases in the years following the menopause. (Konds et al 1990). Oestrogen has been used to treat postmenopausal urgency and urge incontinence for a number of years but there have been very few controlled trials perfomed to confirm that it is of benefit. In a double blind multicentre study of patients with the "urge syndrome" 64 postmenopausal women were treated with oral oestril 3 mg daily or placebo for 3 months. (Cardozo et al, 1993). Compliance was confirmed by a significant improvement in the maturation index of vaginal epithelial cells in the active but not the placebo group. Oestriol produced subjective and objective improvements in urinary symptoms but it was not significantly better than placebo. In a further study sustained release 25mg 17b-oestradiol vaginal tablets (Vagifem, Novo Nordsk) or placebo were used to treat 110 postmenopausal women. Urodynamic investigations confirmed that the women had either sensory urgency, detrusor instability or a normal study. At the end of the 6 month treatment period the only significant differences between the active and placebo groups was an improvement in the symptom of urgency in the women who had a diagnosis of sensory urgency. It is possible that this low dose of local oestrogen was reversing atrophic changes in the lower urinary / genital tract rather than treating the underlying pathology.

These studies may not have shown any benefit possibly because the wrong type of oestrogen was used for too short a time period or it may have been given by the wrong route. Estriol, although a naturally occurring oestrogen, has little effect on the endometrium and does not prevent osteoporosis. It is therefore also questionable whether the low dose used in these studies is sufficient to treat urinary symptoms. Sustained release 17B-oestradiol vaginal tablets are well absorbed and have been shown to induce maturation of the vaginal epithelium within 14 days but higher systemic levels may be needed for therapy to alleviate lower urinary tract symptoms.

Recurrent urinary tract infections

Following the menopause changes in vaginal flora occur which place women at increased risk of urinary tract infections, particularly if they are sexually active. There is a rise in vaginal pH and fall in the number of lactobacilli, allowing colonization with gram negative bacteria which act as uropathogens. These changes are reversed by oestrogens, an effect which enables it to be used for treatment or prophylaxis. In the largest double blind study to date Raz and Stamm (1993) Randomized 93 postmenopausal women with recurrent urinary tract infections to intravaginal oestriol cream or a placebo. Midstream urine cultures were obtained at enrolment, monthly for eight months and whenever urinary symptoms occurred. The incidence of urinary tract infections in the group given oestriol fell significantly as compared with the group given placebo (0.5 vs. 5.9 episodes per patient per year). Unfortunately, we have been unable to reproduce these results in a double blind placebo controlled study of oral oestriol in the prevention of recurrent urinary tract infections in elderly women. (Cardozo et al 1998). Although both oestriol and placebo improved urinary symptoms during the trial, the incidence of urinary tract infection did not differ significantly between the two groups.

Conclusion

Oestrogen deficiency has been implicated in the pathogenesis of a wide range of urogenital complaints. Although its role in the treatment of atrophic vaginitis appears to be established the place of hormone replacement for urinary problems is less clear. Oestrogens when given alone do not objectively improve urinary incontinence but they may be more effective when used in combination with other treatments. Some evidence suggests that oestrogens may provide propbylaxis against recurrent urinary tract infections but the "best" route of therapy, type of oestrogen and duration of therapy are at present unknown.

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