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UROGENITAL ATROPHY IN CLIMACTERIC WOMEN: MENOPAUSE OR GERIPAUSE?

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ABSTRACT

Deterioration of pelvic support and urinary and fecal control in women occurs after the menopause but it is not clear whether these manifestations are age or hormone related.

Furthermore, it is not known whether estrogen deficiency after the menopause accelerates the adverse effects of biological ageing on female pelvic support and urinary and fecal continence mechanisms. This hypothesis can be tested in a female rat animal model with a long life span (Fischer 344) after ovariectomy and postoperative administration of estrogen and/or growth hormone releasing peptide (hexarelin) that has an anti-ageing effect, or no intervention. The results can be compared between aged and young adult rats using functional and morphological assessments at different hierarchical levels. These include the indicators of estrogen deprivation at the menopause such as amount and distribution of collagen fibres types I and III, number of vascular plexus in the urethral and anal canal submucosa, expression of estrogen receptors in the pelvic floor, urethra

and anal canal and amount or relative distribution of muscle fibre types and the specific cellular markers of ageing such as expression of cytoplasmic p27kip1 protein in the pelvic floor and the urethral and anal sphincter muscles. This work may assist in understanding changes caused by biological versus reproductive senescence of the pelvic floor with a potential for improved and preventive therapeutic interventions in the climacteric population.

Key Words: Ageing, estrogen, female, menopause, pelvic floor, rat.

INTRODUCTION

The study of the menopause has received much attention recently for two main reasons. The first is the increased life expectancy of women and of subsequent postmenopausal manifestations. In the United Arab Emirates [UAE], for example, the median age of natural menopause is 48 years (mean = 47.3 ± 3.3, range = 40-59) and the average life expectancy of UAE women is 76.2 years . The improved health services and recent affluence in the country allows for UAE women to live longer and therefore experience postmenopausal complications during approximately one third of their life span 1. The second reason is the current medical and public concern about the serious adverse effects of hormone replacement therapy in postmenopausal women as reported in the Women's Health Initiative Trial 2.

In particular, there is considerable interest in the recent literature concerning the deterioration of pelvic support and urinary and fecal control in women after the menopause 3-6. Although it is generally assumed that these manifestations are related to a fall in circulating estrogen levels at the time of menopause, changes due to the ageing process itself cannot be excluded. Furthermore, the contribution of age as independent risk factor for pelvic floor dysfunction in climacteric women is rarely, if ever, described in Anatomy or Physiology texts. We have also been unable to locate a discussion of this subject in monographs about female pelvic floor disorders in Urogynecology or Colorectal texts 7,8. In contrast, changes induced by ageing are widely appreciated in the pathogenesis and management of other degenerative geriatric disorders in women such as bone, joint and neurological diseases 9.

HYPOTHESIS

To date, the relationship between the pure effects of estrogen deficiency as opposed to normal ageing on the functions of the pelvic floor and urinary and fecal control after the menopause has rarely been studied in elderly women. Presence of the characteristic changes of ageing in the pelvic floor and /or the lower urinary and gastrointestinal tracts and the ability of these changes to induce structural or functional defects in individual components of pelvic support apparatus would provide evidence for non-estrogen-mediated effects on the pelvic floor in postmenopausal women.

The hypothesis that estrogen deficiency after the menopause accelerates the adverse effects of biological ageing on pelvic support and urinary and fecal continence mechanisms in climacteric women needs further investigation. These effects can be studied in a female animal model with a long life span after ovariectomy (castration) and postoperative administration of estrogen and/or growth hormone releasing peptide, hexarelin [HEXA], replacement or no intervention. Hexarelin is a synthetic growth hormone releasing hexapeptide that reverses the effects of ageing in experimental animals 10. HEXA can be administered to confirm that it can reverse the ageing process using several indicators. One of these is the p27kip1 protein, a cycline-dependent kinase inhibitor required for cell cycle arrest that plays an important role in the regulation of skeletal muscle differentiation and apoptosis. Elderly postmenopausal patients with pelvic floor disorders show strong expression of cytoplasmic p27 in the pelvic floor muscle cells associated with shrinking and fragmentation of the cells compared to younger patients 11.

The classical indicators of estrogen deprivation to the pelvic floor at the menopause include amount and distribution of collagen fibres types I and III and number of vascular plexus in the urethral and anal canal submucosa, expression of estrogen receptors in the pelvic floor, urethra and anal canal and amount and distribution of muscle fibre types in the pelvic floor muscles, urethral and anal sphincters 3-6.

BACKGROUND

Pelvic floor disorders such as pelvic organ prolapse, urinary incontinence and fecal incontinence are prevalent conditions in elderly women causing significant physical and psychological morbidity with obvious detriment to social interactions, lifestyle, emotional well-being and overall quality of life 13-15. These disorders occur as a result of weakness of the connective tissue and muscular support of pelvic organs due to a number of factors mainly vaginal childbirth. There is also a consistent increase in the incidence of female pelvic floor disorders after the cessation of reproductive function but it is not clear whether this represents an age- or hormone- related phenomenon 11, 13-17.
In the last two decades, several animal and human studies have shown the presence of estrogen receptors in the urinary bladder, urethra, external anal sphincter and levator ani muscles and other pelvic support ligaments 18-23. This finding provided evidence for a direct action of estrogens on different components of the female pelvic floor that was subsequently considered important in the pathogenesis and management of pelvic floor disorders in postmenopausal women 3-6,11,17. Anatomical data simultaneously revealed that the morphology of pelvic floor musculature is estrogen-dependent since histometric studies have shown that in females, type I muscle fibers were larger than type II 24. This is the reverse of the normal relationship of the diameters of these two histochemical fiber types in all other striated muscles studied in men or women. Epidemiological research further supported this hypothesis because the prevalence of pelvic floor weakness showed a female to male preponderance of 8:1 at the climacteric with a possible benefit of estrogen replacement therapy in affected postmenopausal women 13-15,17. Recent meta-analyses, however, found that estrogen therapy alone was not an effective treatment for

postmenopausal pelvic floor disorders but may have a role when combined with other therapies 11,25,26.

There is presumptive morphological and physiological evidence that the process of ageing might be involved in pelvic floor weakness and impaired urinary and fecal control at the climacteric in addition to the effects of estrogen deficiency 9,11,15,17,27-35. However, the relative contribution of each factor to pelvic floor dysfunction has rarely been investigated in postmenopausal women 11,30-36. The use of female rats as animal models to study normal pelvic floor function and structure as well as experimentally induced dysfunctions such as castration- and ageing- related changes is well established because of their unique properties 31,33-41. In particular, virgin female Fischer 344 rats (Harlan Industries, Indianapolis, Indiana, USA) seems an ideal choice because the mean survival time of animals in this colony is 30 months.

METHODS

A study is urgently needed to ascertain whether biological senescence per say has an additional negative effect on pelvic support components after castration in old female rats with and without estrogen and/or HEXA replacement compared to younger rats subjected to the same intervention. The indicators of ageing can be compared between the control groups of young adult and senescent rats. The ageing effects of estrogen deficiency can be investigated by comparing both the ovariectomized young adult and senescent animals with the senescent control group. The impact of estrogen deprivation can then be confirmed by comparing the effects of administering estrogen to these ovariectomized rats with the senescent control group. The plausible ability of HEXA to reverse the ageing changes can be assessed by comparing the effects of administering HEXA to both the ovariectomized young adult and senescent rats with the young adult control group.

The experiments may include functional and morphological assessments at different hierarchical levels as part of a comprehensive study examining the pelvic floor.

1. At the tissue level: whether administration of estrogen and/or HEXA influences the amount or distribution of collagen fibres types I and III and the number of vascular plexus in the urethral and anal canal submucosa as well as the amount or relative distribution of muscle fibre types in the pelvic floor and the urethral and anal sphincter muscles of ovariectomized aged and young adult rats.
2. At the cellular level: whether administration of estrogen and/or HEXA affects the expression of estrogen receptors in the pelvic floor, urethra and anal canal of ovariectomized aged and young adult rats.
3. At the molecular level: whether administration of estrogen and/or HEXA affects the expression of specific cellular markers of ageing such as cytoplasmic p27kip1 protein in the pelvic floor and the urethral and anal sphincter muscles of ovariectomized aged and young adult rats. Potential application

It has been suggested that the symptomatology of the climacteric may be a culture-bound phenomenon. Our previous results, however, showed that it is experienced by women in the UAE despite the differences in culture and in ambient temperature 1. The expression

of human climacteric, therefore, appears to be a universal biological phenomenon. Urinary incontinence was admitted frequently in this study indicating that such problem is common yet underreported in UAE women after the menopause 1.

We recommended a study to test the hypothesis that estrogen deficiency after the menopause accelerates the adverse effects of biological ageing on female pelvic support and urinary and fecal continence mechanisms. This work may provide evidence for a possible role of ageing on pelvic floor support and urinary and fecal control in climacteric women. This knowledge may assist in understanding changes caused by biological versus reproductive senescence with a potential for improved and preventive therapeutic interventions in the climacteric patient population.

REFERENCES

1. Rizk DEE, Bener A, Ezimokhai M, Hassan M, Micallef R. The age and symptomatology of natural menopause among United Arab Emirates women. Maturitas 1998; 29: 197-202.
2. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002; 288: 321-333.
3. Hextall A, Cardozo L. The role of estrogen supplementation in lower urinary tract dysfunction. Int Urogynecol J 2001; 12: 258-261.
4. Chaliha C, Kullar V. Urinary incontinence: epidemiology and aetiology. Curr Obstet Gynaecol 2000; 10: 60-65.
5. Cardozo LD, Kelleher CJ. Sex hormones, the menopause and urinary problems. Gynecol Endocrinol 1995; 9: 75-84.
6. Donnelly V, O'Connell RR, O'Herlihy C. The influence of oestrogen replacement on faecal incontinence in postmenopausal women. Br J Obstet Gynaecol 1997; 104: 311-315.
7. Bent AE, Ostergard DR, Cundiff AW, Swift SE. Ostergard's Urogynecology and Pelvic Floor Dysfunction, 5th edition, Philadelphia, J.B. Lippincott Company, 2002.
8. Gordon PH, Nivatvongs S. Principles and practice of surgery for the colon, rectum and anus. 2nd edition. New York: Marcel Dekker Inc., 1999.
9. Verelst M, Maltau JM, Orbo A. Computerised morphometric study of the paraurethral tissue in young and elderly women. Neurourol Urodynam 2002; 21: 529-533.
10. Settembrini BP, Figueroa JM, Gallardo MR, Chiocchio SR. Growth hormone (GH) but not IGF-I secretion is stimulated in aged rats by chronic hexarelin and GHRP-6 administration. Endocrine Regulations 1998; 32: 17-26.
11. Bukovsky A, Copas P, Caudle MR, Cekanova M, Dassanayake T, Asbury B, et al. Abnormal expression of p27kip1 protein in levator muscle of aging women with pelvic floor disorders- a relationship to the cellular differentiation and degeneration. BMC Clin Pathol 2001; 1: 4.

12. Hayflick L. Theories of biological aging. Exp Geront 1985; 20: 145-159.
13. Fornell EU, Wingren G, Kjolhede P. Factors associated with pelvic floor dysfunction with emphasis on urinary and fecal incontinence and genital prolapse: an epidemiologic study. Acta Obstet Gynecol Scand 2004; 83: 383-389.
14. Diokno AC. Epidemiology and psychosocial aspects of incontinence. Urol Clin N Am 1995; 22: 481-485.
15. Sangwan YP, Coller JA. Fecal incontinence. Surg Clin N Am 1994; 74: 1377-1398.
16. Jameson JS, Kamm MA, Speakman CT, Chye YH, Henry MM. Effects of age, sex, and parity on anorectal function. Br J Surg 1994; 81: 1689-1692.
17. Brown JS. Epidemiology and changing demographics of overactive bladder: a focus on postmenopausal woman. Geriatrics 2002; 57 (Suppl 1): 6-12.
18. Iosif CS, Batra S, Ek A, Astedt B. Estrogen receptors in the human urinary tract. Am J Obstet Gynecol 1981; 141: 817-820.
19. Haadem K, Ling L, Ferno M, Graffner H. Estrogen receptors in the external anal sphincter. Am J Obstet Gynecol 1991; 164: 609-610.
20. Smith P, Heimer G, Norgen A, Ulmsten U. Localization of steroid hormone receptors in the pelvic muscles. Eur J Obstet Gynecol Reprod Biol 1993; 50: 83-85.
21. Mokrzycki ML, Mittal K, Smilen SW, Blechman AN, Pogers RF, Demopolous RI. Estrogen and progesterone receptors in the uterosacral ligament. Obstet Gynecol 1997; 90: 402-404.
22. Lang JH, Zhu L, Sun ZJ, Chen J. Estrogen levels and estrogen receptors in patients with stress urinary incontinence and pelvic organ prolapse. Int J Gynaecol Obstet 2003; 80: 35-39.
23. Moalli PA, Talarico LC, Sung VW, Kilngensmith WL, Shand SH, Meyn LA, et al. Impact of menopause on collagen subtypes in the arcus tendineous fasciae pelvis. Am J Obstet Gynecol 2004; 190: 620-627.
24. Beersiek KF, Parks AG, Swash M. Pathogenesis of anorectal incontinence; a histometric study of the anal sphincter musculature. J Neurol Sci 1979; 42: 11-127.
25. Fantl JA, Bump RC, Robinson D, McClish DK, Wyman JF. Efficacy of estrogen supplementation in the treatment of urinary incontinence. Obstet Gynecol 1996; 88: 745-749.
26. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T, for the Research Group. Postmenopausal hormones and incontinence: the heart and estrogen/progestin replacement study. Obstet Gynecol 2001; 97: 116-120.
27. Otto LN, Slayden OD, Clark AL, Brenner RM. The rhesus macaque as an animal model for pelvic organ prolapse. Am J Obstet Gynecol 2002; 186: 416-421.
28. Levy BJ, Wight TN. Structural changes in the aging submucosa: New morphologic criteria for the evaluation of the unstable human bladder. J Urol 1990; 144: 1044-1055.
29. Elbadawi A, Diokno AC, Millard RJ. The aging bladder: morphology and urodynamics.World J Urol 1998; 16 (Suppl 1): S10-S34.

30. Goepel C, Hefler L, Methfessel HD, Koelbl H. Periurethral connective tissue status of postmenopausal women with genital prolapse with and without stress incontinence. Acta Obstet Gynecol Scand 2003; 82: 659-664.
31. Lluel P, Palea S, Barras M, Grandadam F, Heudes D, Bruneval P, et al. Functional and morphological modifications of the urinary bladder in aging female rats. Am J Physiol 2000; 278: R964-R972.
32. Zhu Q, Resnick NM, Elbadawi A, Kuchel GA. Estrogen and postnatal maturation increase caveolar number and caveolin-1 protein in bladder smooth muscle cells. J Urol 2004; 171: 467-471.
33. Tannenbaum C, Perrin L, Kuchel GA. The aging pelvic floor. In: Crocos J, Schick E, editors. The Urinary Sphincter. New York: Marcel Dekker Inc.; 2001: 175-181.
34. Zhu Q, Ritchie J, Marouf N, Dion SB, Resnick NM, Elbadawi A, et al. Role of ovarian hormones in the pathogenesis of impaired detrusor contractility: evidence in ovariectomized rodents. J Urol 2001; 166: 1136-1141.
35. Plas E, Pfluger H, Maier, Hubner W. The Aging Bladder. Wien New York: Springer-Verlag; 2004.
36. Zapantis G, Santoro N. Ovarian ageing and the menopausal transition. Best Pract & Res Clin Obstet Gynaecol 2002; 16: 263-276.
37. Levin RM, Malkowics SB, Wein AJ. Laboratory models for neuropharmacologic studies. World J Urol 1984; 2: 222-233.
38. Rizk DEE, Mensah-Brown EP, Chandranath SI, Ahmed I, Shafiullah M, Patel M, et al. Effects of ovariectomy and hormone replacement on collagen and blood vessels of the urethral submucosa of rats. Urol Res 2003; 31: 147-151.
39. Rakoczy PE, Zhang D, Robertson T, Barnett NL, Papadimitriou J, Constable IJ, et al. Progressive age-related changes similar to age-related macular degeneration in a transgenic mouse model. Am J Pathol 2002; 161: 1515-1524.
40. Yiou R, Delmas V, Carmeliet P, Gherardi RK, Barlovatz-Meimon G, Chopin DK, et al. The pathophysiology of pelvic floor disorders: evidence from a histometric study of the perineum and a mouse model of rectal prolapse. J Anat 2001; 199: 599-607.
41. Sartori MG, Girao MJ, de Jesus SM, Sartori JP, Baracat EC, Rodrigues G. Quantitative evaluation of collagen and muscle fibers in the lower urinary tract of castrated and under-hormone replacement female rats. Clin Exp Obstet Gynecol 2001; 28: 92-96.