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EDITORIAL

Ageing of the female pelvic floor: towards treatment *a la carte* of the "geripause"

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When you are old and grey and full of sleep,
And nodding by the fire, take down this book,
And slowly read, and dream of the soft look,
Your eyes had once, and of their shadows deep.
William Butler Yeats (1865–1939)

The study of menopause and female ageing "geripause" is receiving much attention lately from the health care community for three main reasons [1–3]. The first is the global increase in female life expectancy as a result of improved health awareness and services with continuing reduction of adult mortality, progressive transition from high to low fertility, and recent socioeconomic affluence in most countries. This unprecedented demographic change, which started in the developed world in the 19th century and more recently in developing countries, allowed women to experience menopausal manifestations during approximately one third of their lifespan and reach the geripause. Secondly, the process of medicalization within the broader context of the dominance of health as a cultural preoccupation in recent societies and women's motivation by personal concerns and cultural forces to take more control of the effects of menopause and/or ageing on their bodies has resulted in increasing use of female sex hormones as a replacement therapy. Finally, there is a growing public and medical concern about the serious adverse effects of estrogen/progestin replacement therapy in old postmenopausal "geripausal" women that had been recently reported in the Women's Health Initiative Trial. This is accompanied by considerable interest in the contemporary biomedical literature, in particular, about the prevalence, detrimental effects, and management of support-related pelvic floor dysfunction (pelvic organ prolapse, urinary incontinence, and fecal incontinence) in the geripausal population. There seems to be no consensus, however, whether the exact underlying mechanism is normative ageing, falling circulating estrogen levels caused by menopausal ovarian failure, or a combination of both factors [3–9].

It is widely believed that estrogen deprivation at the climacteric is primarily responsible for support-related pelvic floor dysfunction in geripausal women. This assumption is based on the detection of estrogen receptors in the components of continence-maintaining and supportive pelvic floor structures in premenopausal women and experimental animals [3–6]. In turn, estrogen replacement had been extensively used to prevent or restore the decline in pelvic floor support and/or deterioration of urinary and fecal control after the menopause but without critical analysis of the long-term cure rates or evidence-based improvement in clinical outcome after treatment in most studies [7]. Paradoxically, a recent meta-analysis and a

This article is dedicated to the memory of Dr. Hazem A. Hassan, Ph. D., Associate Professor of Biology, Faculty of Science, United Arab Emirates University, who died during the animal experiments before preparation of this manuscript.

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large prospective randomized control trial showed that estrogen replacement therapy significantly increased the risk and severity of urinary incontinence in continent and symptomatic postmenopausal women, respectively [7, 8]. Systematic review of current epidemiological studies and surgical series also consistently found that age is by far one of the strongest predictors of female support-related pelvic floor dysfunction or treatment failure, respectively, while the role of menopause remains uncertain [9, 10].

It is not usually appreciated that there are widespread and age-related biological changes, independent of the altered ovarian hormonal milieu of the menopausal transition, that contributes to the adverse chronobiological effects on different tissues in geripausal women [3–6]. In addition, morphological, physiological, and clinical data indicate that specific "intrinsic" ageing changes in the pelvic floor superimposed on extrinsic estrogen deficiency could be responsible for the decreased integrity observed in geripausal women [3–6, 11, 12]. Hence, a *bona fide* adverse biogerontologic effect on the postmenopusal pelvic floor cannot be excluded. Surprisingly, we have been unable to locate a discussion of this simple and logical assertion in monographs about female pelvic floor disorders in gynecology, urology, urogynecology, or colorectal texts. In contrast, changes induced by ageing are widely accepted as an underlying risk factor in the pathogenesis of other degenerative female geriatric disorders such as bone, joint, musculoskeletal, cardiovascular, and neurological diseases [13].

Geripausal women can be viewed as a natural model *par excellence* for determining the pure effects of ageing (biological senescence) and menopause (reproductive senescence) on pelvic floor supportive function as two independent dichotomous covariates, both in the absence and presence of estrogen replacement. Laboratory animals, which are old and those with surgically induced ovarian failure (ovariectomy), are very useful proxy models to study this observation by circumventing several extraneous and confounding variables inherent in clinical studies [3–6]. Although the human pelvic floor may differ structurally from that of quadrupeds, the anatomy of the urethra, anal canal, and pelvic floor muscles in the female rat is sufficiently similar *in toto* to that of the human female to serve as a model for morphologic experimental studies [14]. Murine models are also widely available, cheaper, and can be bred locally in contrast to the classical primate or canine models of pelvic floor studies like the rhesus macaque, squirrel monkeys, and beagles [15, 16]. Fisher 344 rats are particularly suitable for ageing research, because the mean survival time of this colony is prolonged (30 months) compared to other rat models [5]. More importantly, puberty occurs between 2 and 4 months of age in females, while ageing changes start around 15–16 months of age despite their long average lifespan. This allows studying the effects of ovariectomy-induced estrogen deprivation and ageing in various pelvic floor tissues over a wider age range in female Fisher 344 rats [5, 14].

Ageing is a complex and evolutionary spectrum of innate and progressive events affecting molecules, cells, and the whole organism that is theoretically caused by release of free radicals, non-enzymatic glycosylation, and apoptosis [13]. The whole process is presumably under the control of the endocrine systems mainly growth hormone (GH), estrogens, and androgens with significant gender differences in the pace of development of ageing changes in some organs [17]. For example, there is greater deterioration in structure, function, and metabolism of the brain in females than in males. GH is thought to have an important anti-ageing function in humans, because the circulating levels show age-related changes with remarkable increase at puberty and gradual decline with advancing age [3]. GH and its releasing stimulants/agonists are thus widely used in clinical and experimental ageing research to reverse the effects of ageing. The most potent GH secretagogue is ghrelin, a recently discovered 28 amino acid peptide hormone isolated from the rat and human stomach [18–22].

The morphological surrogate biomarkers of ageing and/or estrogen deficiency in the pelvic floor include the relative proportion of urethral and anal canal submucosal collagen fibers types I and III and of striated pelvic floor muscles (striated urethral and anal sphincters and the levator ani) isomyosin fibers types I and II and the number of urethral and anal canal submucosal vascular plexuses [3–6, 15, 16]. Changes in type I to III collagen ratio correlates with changes in the tissue mechanical properties, because type I is more rigid, while type III contributes more to elastic properties [6]. Decreased collagen I/III ratio in the urethral and anal canal submucosa is, therefore, associated with reduced closure function [15]. The number of submucosal vessels is an important component of, and is directly related to, intrinsic urethral and anal canal sphincter function maintaining positive closure pressure and continence in women [3]. Both estrogen deficiency and ageing independently and negatively influence the submucosal urethral and anal canal collagen I/III ratio and blood vessel counts in anatomical, experimental, and clinical studies [3, 5, 6, 15]. The proportion of type I (slow) to type II (fast) isomyosin muscle fibers determines muscle strength and contractile characteristics [5, 6]. A higher proportion of isomyosin I/II in the levator ani occurs after ovariectomy in rats and with ageing in women, and this is associated with urodynamic urinary incontinence [5, 6].

At the ultrastructural level, distinct changes are also observed with ageing in the pelvic floor. Satellite cells and mitochondria are quiescent precursor elements of the myofibers whose number represent the capacity for self-repair and regeneration of striated muscles including pelvic

floor muscles in response to ageing [23]. Cytoplasmic expression of $p27^{kip1}$ in these muscles is also considered a specific biochemical marker of ageing, because this protein normally regulates skeletal muscle cell differentiation and apoptosis [4]. Significant depletion of satellite cells and mitochondria per muscle cell is observed in the levator ani of senile rats and in elderly postmenopausal women with pelvic organ prolapse compared to juvenile rats and women without prolapse, respectively [11]. Elderly postmenopausal women with urinary or fecal incontinence show strong expression of cytoplasmic $p27^{kip1}$ in the levator ani muscle cells associated with cell shrinking and fragmentation compared to younger postmenopausal or premenopausal patients [4, 5].

Presence of the characteristic ageing changes in the individual components of pelvic floor support apparatus and the ability of anti-ageing agents to reverse these changes would provide evidence for non-estrogen-mediated effects on the pelvic floor in geripausal women [15, 16]. We tested this hypothesis in a series of in vivo animal experiments performed on virgin female Fisher 344 rats [5, 6]. We compared the pre- and postoperative effects of ovariectomy with or without postoperative administration of estrogen, ghrelin, or both hormones on biomarkers of ageing of the pelvic floor in old (18 months old) versus young adult (3 months old) rats. We found that the natural and expected change in expression of all biomarkers of ageing in the urethra, anal canal, and striated pelvic floor muscles of old rats is increased further after ovariectomy compared to young adult animals. Estrogen replacement was not sufficient to reverse these post-ovariectomy adverse changes in old rats in contrast to young adult rats. In old rats, the changes were restored to pre-ovariectomy levels only by adding the anti-ageing drug, ghrelin, to estrogen.

A possible explanation for our pooled experimental findings was that ageing of the female pelvic floor is similar to cognitive function that gradually declines with ageing but is often accelerated in women after menopause [3–6]. Both estrogen and ghrelin influence the secretion of GH, FSH, and LH and vice versa, but it is not clear whether this occurs via positive or negative feedback mechanism [18, 19]. The interrelationship between the effects of ageing and menopause on the pelvic floor, therefore, is not entirely clear and may be mediated by direct interaction with estrogen/ghrelin receptors or secondary to interplay between estrogen/ghrelin and other pituitary hormones [3–6]. Likewise, the menopausal and ageing effects on the pelvic floor needs further investigation at the cyto-molecular level, because this appears to be tissue and organ specific and depends on target organ ghrelin/estrogen receptor subtypes or density variation and connective tissue or muscular fiber type composition. Furthermore, the outward manifestations of tissue ageing in the elderly results primarily from molecular mechanisms such as cross-linking and side-chain modifications involving the major structural proteins of the body. Unraveling these mechanisms instead of studying changes in the tissue morphological changes or physical properties as a result of ageing will ultimately lead to the development of inhibitors of the deleterious effects of ageing. This work is now in progress.

The hypothesis that estrogen deficiency after the menopause accelerates the adverse effects of biological ageing on pelvic floor support mechanisms in geripausal women thus seems plausible. To date, this concept, however, has not been adequately studied. Although there are differences between rats and humans regarding functional pelvic floor topography, physiology of continence, pelvic organ support, and function of the ghrelin system, the proof of concept of independent and non-estrogen-mediated ageing changes of the pelvic floor and the ability of ghrelin to reverse these changes was achieved in our animal model with these data [3–6]. Therefore, we believe that our results should be examined in phase 2 and 3 clinical studies to investigate the full therapeutic potential of ghrelin and suggest close collaboration between urogynecologists and gerontologist in this endeavor. We recommend a pilot placebo-controlled study *ab initio* to examine the relation between ghrelin, estrogen, and the surrogate biomarkers of ageing/menopause in geripausal versus young premenopusal women with support-related pelvic floor dysfunction. The study specimens could be obtained by a direct biopsy from the easily accessible human urethra, anal canal, or pelvic floor muscles. Site of collection of tissue specimens should be standardized, however, to include the key pelvic floor muscle elements of interest and avoid potential bias resulting from sampling different pelvic muscle groups [3, 15, 16]. Less invasive routes for ghrelin administration should be also tested, because the hormone is only effective upon intravenous injection [20–22]. Ideally, tissue from a control group of age-matched women without dysfunction should be compared with diseased women. However, it would not be ethical or physiological to take samples from the target organs of interest from healthy women or those presenting with other gynecologic conditions, respectively [24]. A proposal to obtain fresh strips of these tissues from postmortem controls could be a possible solution.

Enigmatically, most of the information that we need to know in clinical medicine seems obvious, but the obvious is often unnoticed merely because it is simple. Ageing of the female pelvic floor is a case in point because the two historical perils of scientific inquiry—*nullius in verba*, take nobody's word for granted and *principium scientiae simplex*, scientific principles are simple—are frequently overlooked. Hence, there is a significant biomedical knowledge gap about the complex and changing relation-

ships between menopause and female ageing that is stereotyped by media portrayal and lay perceptions of both processes as synonymous. Although a constructive dialogue between sociologists and biologists is needed in the long term, geripause-induced pelvic floor dysfunction is expected to increase in the near future, because the female population of most countries of the world including developing countries is ageing. Because we have a shorter time to understand these adverse changes as the count down has already begun, it is urgent that the international urogynecologic society begin taking steps to face the geripausal challenge and ascertain the extent and depth of this problem. Medical science is now well-paced to make substantial and avant-garde contributions to the management of geripausal pelvic floor disorders notwithstanding the fact that a woman's programmed biological age or natural reproductive span could not be reversed. There has been little progress in this field, however, partly because of ethical constraints associated with experimental studies in women and using human tissue. Animal models like our own can offer an ideal testing system for investigating the pathogenesis of ageing of the female pelvic floor and for conducting further targeted therapeutic human studies on hypotheses validated in animals [24]. The research mandate is to identify safe, effective, and disease-specific *a la carte* pharmacological intervention for geripausal women with support-related pelvic floor dysfunction as a supplement or substitute to estrogen replacement [7–12].

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Conflicts of interest None.

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