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The ageing woman

Invited editorial

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When does (sexual) ageing begin? Ageing is the natural progression of changes in structure and function that occurs with the passage of time in the absence of known disease [1]. Women experience *reproductive aging* (hypothalamic-pituitary-ovarian axis) superimposed on *chronological aging*. Reproductive aging begins at birth, with the progressive destruction of the oocyte's reserve, and proceeds as a continuum. It reaches an essentially non-functional state (menopause) much earlier than other body systems and at a time in which women are otherwise healthy [1]. Much of the research on the relative effects of reproductive aging has focused on menopause [2-6].

Sexual aging has a different starting time, due to the interplay between the biological event of puberty and the psychosocial factors modulating the adolescence's process. Biologically speaking, the early twenties seem to coincide with the optimal sexual function in women, unless negative psychosexual and/or context-related factors, such as a negative or sexually restricted upbringing, were in play. Both total and free testosterone, and dehydroepiandrosterone, powerful biological initiators and modulators of sexual response in women as well as in men, peak in women by the age of twenty. At forty, the plasmatic levels of these hormones are on average half of those women have at twenty [5].

Epidemiological data suggest that age has a negative effect on women's sexuality, from the twenties onwards [3,4]. The *probability of having sexual dysfunctions increases with age*, with different percentages according, among others, to the sociocultural background. Protective factors, modulating the impact of age, are: being married, employed, having a good personal/family income, high education, a satisfying sexual life during the fertile age, and, last but not least, having access to qualified medical care. The *distress* associated with decreasing sexual function, specifically evaluated for loss of desire, is *inversely correlated with age* [2-4]: the younger the women, the higher the probability that the sexual dysfunction will be perceived as negatively affecting self-esteem, self-image and the quality of the relationship. In a recent European survey, 63% of women younger than 50 who complained of loss of desire felt very concerned because they "were letting their partner down".

Menopause has a further detrimental effect. Its impact on sexual function is associated to the loss of sexual hormones and the severity of menopausal symptoms [2-6]. A recent cross sectional survey, on 4517 women, aged 20-70, recruited from market research panels in USA, UK, Germany, France and Italy, indicates that symptoms more related to markers of menopausal hormonal change are: hot flashes, night sweats, poor memory, difficulty sleeping, aches neck, head and shoulders, vaginal dryness and difficulty with sexual arousal [3]. Physical and mental morbidity affect perception of all symptoms.

Surgical menopause, due to removal of both ovaries, with the parallel loss of estrogens and more than fifty per cent of total testosterone of the female body, anticipates and worsens the impact of age on women's sexual ageing, unless appropriate hormonal therapy [HT] is initiated [2-6].

Partner's sexual and general health problems appear to be the most important context-related predictors of women's sexual changes across the menopause and beyond.

Health expectancy vs life expectancy

Women get (sexually) old very differently from one another. Their *health expectancy* may be much shorter than their *life expectancy*, the difference being again modulated by biological, psychosexual and context-related factors [2]. Ideally, medicine should aim at reducing this gap up to lead health expectancy to coincide with life expectancy.

From the clinical point of view, physician may greatly impact on women's quality of aging, from the general health and sexual point of view. More so if they identify four key signs of menopausal vulnerability to high risk sexual aging. These signs are easy to be checked in the clinical setting, with no extra costs for the patient nor for the public health system.

DRAFT COPY – PERSONAL USE ONLY**Clinical predictors of high risk sexual aging**

Accurate clinical history and physical examination should consider at least four key symptoms and signs:

a) age at menopause

The earlier the age, the worse the impact on general health and sexual well-being [2,6]. Premature menopause (PM), either spontaneous (Premature Ovarian Failure, POF) or iatrogenic (surgical bilateral oophorectomy, chemotherapy, pelvic or total body radiotherapy) anticipates the multisystemic ageing process, with a potential more negative effect, according to the phase of the reproductive life-stage it happens. Spontaneous ovarian failure affects on average 1% of women under 40 years of age, although percentages as high as 7.1% have been recently reported. Iatrogenic menopause, for benign and malignant conditions, affects 3.4-4.5% of women under 40 and up to 15% between 40 and 45 years of age [6]. The 5-year survival for all malignancies in childhood and adolescence is 72% (up to 90% for some cancers) with an increasing number of survivors facing the challenges of adulthood deprived of their gonadal hormones, unless an appropriate HT for dosage, type and *length of treatment* is prescribed [6-11]. Premature menopause is associated with an accelerated risk of osteoporosis, coronary heart disease and Alzheimer disease, i.e. of earlier pathological aging. Distressing sexual disorders are more frequently reported in women with PM [2-3], particularly after bilateral oophorectomy [3,4,12,13]. In PM women, the risk of breast cancer after HT corresponds to the risk found in premenopausal women of similar age who have not suffered an iatrogenic or premature menopause. Consensus therefore exists on the recommendation that women who have undergone premature menopause (unless associated with hormone-dependent cancer, such as breast cancer or genital adenocarcinoma) should be offered HT, *at least until the average age of menopause* (51 years) [7-9]. Asking about the age at menopause focuses the clinician's attention on a powerful marker of pathological general and sexual aging, and stresses as well the need of a more active therapeutic intervention.

b) severity of hot flushes

Considered for decades just as a menopausal nuisance, *hot flushes* are increasingly recognized as critical *neurobiological markers of the vulnerability of the Central Nervous System (CNS)* to loss of sexual hormones and pathological aging [10]. Severe hot flushes are indeed associated with more severe affective disorders (depression and anxiety), loss of sexual desire, sleep disorders and cognitive impairment, with early concentration difficulties and memory loss [2,3,10]. In this perspective, the neurovegetative system can be considered a sensitive, early and reliable marker of the neuronal need of estrogens for their optimal neuroplasticity, predictor of a better nervous and sexual aging. HT, prescribed in the *early* postmenopausal years to relieve women from severe hot flushes, could in parallel delay a more diffuse impairment of the CNS, thus contributing to quality mental (and sexual) aging [10]. However, timing is key. Late HT, beyond the age of 70, may have the opposite effect, as shown in the subset of older subjects in the Women's Health Initiative study [7-10,15].

c) increasing vaginal pH

Vaginal pH is modulated by level of tissue estrogens. In the fertile years it physiologically ranges between 3.5 and 4.5. After the menopause, it increases up to 7.0-7.39, mirroring a progressive urogenital atrophy [2,6,13,14]. It is easy to diagnose, with an in-office vaginal stick applied for a few seconds in the vagina. Vaginal pH:

- 1) modulates the *vaginal ecosystem*, and the dynamic equilibrium between billions of micro organisms. When higher than 5.0, it increases the vulnerability of the vagina to the proliferation of usually minority germs of the Gardnerella family, leading to increase of vaginal leakage and signs of inflammation. pH' increase mirrors as well the increased vulnerability of both the vagina and the bladder to infections from colonic germs (Escherichia Coli, Enterococcus faecalis etc), which cause recurrent postmenopausal vaginitis and cystitis, specially post-coital;
- 2) is a marker of the *genital vascular responsiveness* to sexual stimuli: estrogens are permitting factors for the Vasoactive Intestinal Peptide (VIP), the neurotransmitter that "translates" mental arousal into vaginal congestion and lubrication. High vaginal pH correlates with increasing *vaginal dryness and dyspareunia*;
- 3) is a marker of the increased postmenopausal vulnerability of the bladder to *urgency symptoms*, due to loss of estrogens.

In positive, topical, i.e. vaginal, Estrogen therapy (ET) has proven its efficacy in normalizing the vaginal pH and significantly reducing recurrent cystitis and vaginitis, vaginal dryness and dyspareunia, and urgency symptoms [7-9, 13-15]. ET may therefore well address the *urogenital and sexual comorbidity* that increases with increasing age, unless appropriate ET is prescribed. Long-term treatment is often required as symptoms can recur on cessation of therapy. Every systemic and local HT/ET product is government-approved for this indication.

DRAFT COPY – PERSONAL USE ONLY**d) vulvar dystrophy**

The quality of vulvar ageing is the fourth neglected clinical marker of pathological sexual aging. Vulvar aging, inclusive of the clitoral and vestibular bulb cavernosal bodies, is modulated by the tissue levels of estrogens and androgens. It is further accelerated by inappropriate life styles. Autoantibodies may specifically contribute to the accelerated pathological aging, with whitening of the vulvar epithelium, conglutination of the labia, involution of the clitoris and impaired sexual response to a complete clitoral anorgasmia, typical of the so called "Lichen sclerosus vulvae". Clinical experience indicates that topical testosterone may delay the vulvar ageing and maintain a better sexual response, although controlled studies are still lacking [13].

Conclusion

Ageing is a multisystemic and multifactorial process, which can be improved by appropriate life-long lifestyles and selected medical interventions, when indicated. Menopause represents an acute turning point in the more gradual process of aging. Age at menopause, severity of hot flashes, vaginal pH and quality of vulvar aging are simple to assess and costless markers of women's vulnerability to earlier pathological ageing, general and sexual, increasing the gap between health expectancy and life expectancy. Individually tailored Hormonal Therapy (HT) may significantly reduce - although not eliminate- the negative impact of menopause on the ageing process, the earlier the treatment, the more comprehensive and significant the benefit.

Improvement in doctor's attitudes to cure and care may contribute to women's quality of life in aging, through careful listening of women's symptoms, needs, fears and hopes; early diagnosis of markers of high risk sexual aging; and the appropriate treatment. Last but not least, a thorough understanding that sexual issues are an important part of the clinical consultation should encourage a more systematic diagnostic attention to comorbidities between medical and sexual symptoms, even in the late post menopausal years.

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