

Role of Androgens in Female Genitourinary Tissue Structure and Function: Implications in the Genitourinary Syndrome of Menopause

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ABSTRACT

Introduction: Genitourinary conditions in women increase in prevalence with age. Androgens are prerequisite hormones of estrogen biosynthesis, are produced in larger amounts than estrogens in women, and decrease throughout adulthood. However, research and treatment for genitourinary complaints have traditionally focused on estrogens to the exclusion of other potential hormonal influences.

Aim: To summarize and evaluate the evidence that androgens are important for maintaining genitourinary health in women and that lack of androgenic activity can contribute to the development of symptoms of the genitourinary syndrome of menopause.

Methods: The role of androgens in the pathophysiology, diagnosis, and treatment of genitourinary syndrome of menopause was discussed by an international and multidisciplinary panel during a consensus conference organized by the International Society for the Study of Women's Sexual Health. A subgroup further examined publications from the PubMed database, giving preference to clinical studies or to basic science studies in human tissues.

Main Outcome Measures: Expert opinion evaluating trophic and functional effects of androgens, their differences from estrogenic effects, and regulation of androgen and estrogen receptor expression in female genitourinary tissues.

Results: Androgen receptors have been detected throughout the genitourinary system using immunohistochemical, western blot, ligand binding, and gene expression analyses. Lower circulating testosterone and estradiol concentrations and various genitourinary conditions have been associated with differential expression of androgen and estrogen receptors. Supplementation of androgen and/or estrogen in postmenopausal women (local administration) or in ovariectomized animals (systemic administration) induces tissue-specific responses that include changes in androgen and estrogen receptor expression, cell growth, mucin production, collagen turnover, increased perfusion, and neurotransmitter synthesis.

Conclusion: Androgens contribute to the maintenance of genitourinary tissue structure and function. The effects of androgens can be distinct from those of estrogens or can complement estrogenic action. Androgen-mediated processes might be involved in the full or partial resolution of genitourinary syndrome of menopause symptoms in women. **Traish AM, Vignozzi L, Simon JA, et al. Role of Androgens in Female Genitourinary Tissue Structure and Function: Implications in the Genitourinary Syndrome of Menopause. Sex Med Rev 2018;X:XXX–XXX.**

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Key Words: Testosterone; Dihydrotestosterone; Estradiol; Vulvovaginal Atrophy; Androgen Receptor; Estrogen Receptor

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INTRODUCTION

Menopause and aging are associated with decreased biosynthesis of sex steroid hormones resulting in structural and physiologic changes in the genitourinary tract, including, but not limited to, anatomic alterations in vulvar, clitoral, vestibular, urethral, vaginal, anterior vaginal wall, periurethral (prostate), and bladder tissues.^{1–3} There can be thinning of the epithelium, decreased vascularity, altered smooth muscle structure, and decreased collagen and elastin content. Clinically, symptoms and physical examination findings can include thinning and resorption of the labia, retraction of the introitus with concomitant dyspareunia, genital dryness, loss of vaginal rugae, friable vaginal epithelium with signs of injury (petechiae) and/or inflammation, increased vaginal pH, protrusion and widening of the urethral meatus and urethral sensitivity, urinary frequency and urgency, recurrent urinary tract infections, and decreased lubrication, vaginal or vestibular discomfort, or pain with or without sexual activity.^{4–7} Secondary to these symptoms, there also can be decreased libido and orgasmic response, significantly affecting sexual function. In symptomatic women, these changes can cause significant distress with decreased quality of life^{8,9} and constitute part of the diagnosis for genitourinary syndrome of menopause (GSM).¹ GSM is chronic and progressive, increases in severity over time, and does not improve without treatment.^{1,10}

Sex steroid hormones (androgens, estrogens, and progestins) play an important role in human reproductive and sexual function. In particular, androgens and estrogens are critical physiologic modulators during development and maintenance of genital tissue structure and function.^{1,4–6,11} Despite the longstanding perspective that pathologic conditions affecting female genital and urinary tissues are due to estrogen deficiencies,² the biochemical and physiologic mechanisms regulating sex steroid action in the genitourinary system have not been fully investigated and the role of androgens is unrecognized or underappreciated. This review examines the evidence that androgens contribute to genitourinary health in women and that hormonal insufficiency of androgens and estrogens after menopause can lead to GSM.

METHODS

The International Society for the Study of Women's Sexual Health convened a multidisciplinary and international panel of 14 researchers and clinicians in obstetrics and gynecology, endocrinology, urogynecology, internal medicine, biochemistry, and physiology. During the 2-day conference, participants presented and discussed the current state of knowledge on the pathophysiology, diagnosis, and treatment of GSM and, in particular, the role of androgens in female genitourinary tissues. A working subgroup was designated to develop a scientific report to support a separate clinically focused consensus white paper. The writing team performed literature reviews using the US National Center for Biotechnology Information's PubMed

database on (i) the effects of androgens in female genitourinary tissues; (ii) distinctions between androgenic and estrogenic effects; and (iii) regulation of androgen and estrogen receptors (AR and ER) in premenopausal and postmenopausal women, intact and ovariectomized animals, and animal models of human disease. Selection criteria were based on expert opinion and, whenever possible, preference was given to studies that included human tissues. There were no filters or restrictions on publication date. Because treatment recommendations and efficacy of therapies are not specifically discussed in this review, levels of evidence have not been included.

HORMONAL AND GENITOURINARY CHANGES IN POSTMENOPAUSAL WOMEN

During early childhood, plasma estradiol concentration generally remains below 13 pg/mL and gradually increases during prepuberty and through adolescence.¹² Plasma testosterone concentration in prepubertal girls is lower than 20 ng/dL.¹² During the reproductive years, mean plasma estradiol concentration varies throughout the menstrual cycle in women, ranging from 40 to 350 pg/mL, and mean total testosterone concentration is 35 ng/dL (range = 20–70 ng/dL).^{13,14} In healthy premenopausal women, the vagina has a stratified squamous epithelium composed of 3 cell layers consisting of superficial and intermediate cells with few parabasal cells. Normal proliferation of the epithelium leads to the formation of moist and thick rugae on the mucosal surface of the vagina and glycogen released by exfoliated epithelial cells is hydrolyzed into glucose. Then, glucose is metabolized mainly by lactobacilli into lactic acid, creating an acidic environment (pH = 3.5–4.5) that discourages the growth of pathogenic bacteria and fungi.⁶

During menopause, mean estradiol concentration decreases to 13 pg/mL.¹⁴ Although mean testosterone concentration is decreased slightly to a value of 25 ng/dL,¹⁴ it is important to emphasize that androgen levels progressively decrease throughout adult life.^{15,16} Thus, menopause itself is not associated with dramatic decreases in androgens but postmenopausal women can have significantly less endogenous androgens compared with younger women in their 20s and 30s. Interestingly, the perimenopausal state might be associated with a relatively stable serum concentration of free testosterone due to decreasing SHBG, caused in part by decreased estradiol.¹⁷ The greatest decreases in SHBG levels have been reported to occur from 4 years before and up to 2 years after the final menstrual period.¹⁷

In the absence of sufficient levels of sex steroid hormones, the genitourinary organs essentially return to the structure and function more representative of prepuberty. Vulvar tissue can appear diminished, obliterated, or even fused, and irritation or erythema can be evident.¹⁸ The introitus becomes narrow with a loss of hymenal remnants, the cervix can become flush with the vaginal vault, and pelvic organ prolapse is not uncommon.¹⁸ The vagina can become shortened and narrowed; its surface can

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