New Approach to Declining Androgens and Sexual Apathy in Aging Women

a report by
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Sexual thoughts and fantasies are a joy of life. Sexual desire is fun and a vital part of good health. It is a much appreciated basis for relationships between women and their partners. Sexual apathy is anguishing and distressing; it is a common complaint heard by gynecologists. In older women, androgen production and sexual desire decline in parallel during late reproductive years and continue to decline into post-menopausal years. Because of this parallel, it is logical to link declining androgens and sexual apathy as cause and effect. This logic is supported by the repeated confirmation that declining female sexual desire is aggravated by endocrine dysfunctions that involve loss of androgen effect: oophorectomy, menopausal estrogen replacement, corticosteroid treatment, adrenal insufficiency, and hypopituitarism.

Sexual apathy is distressing. With increasing depression among women, many seek counseling and therapy. Androgens in pharmacologic doses can induce intense sexual desire. Thus, empiric self-medication with androgens has been practiced for years. Recently, however, well-documented connections between declining androgen production in women and loss of sexual desire have become established as an area of disciplined scientific inquiry. Furthermore, restoration of sexual desire following androgens in doses approximating pre-menopausal physiology has been achieved in well-designed clinical trials.

This article examines androgen treatment for decreased sexual desire in aging women. It evaluates new approaches, both available and investigational, to treat these women.

Declining Androgens and Aging in Women

Declining androgen production with aging is well documented.[1,2] The topic has been reviewed previously by the author.[1,2] Clinically relevant androgens in women include dehydroepiandrosterone (DHEA), its sulfoconjugate DHEA sulfate (DHEAS), and testosterone. DHEAS is a prohormone that originates almost exclusively from the zona reticularis, or innermost zone, of the adrenal cortex. The zona reticularis contains steroidogenic architecture that is uniquely configured to secrete substantial amounts of DHEAS.[1,2]

Production of DHEAS ranges from 5mg to 40mg per 24 hours, an amount that greatly exceeds almost all other steroid hormones. DHEAS circulates in a large, slow-turning pool at concentrations that are 100- to 1,000-fold higher than unconjugated androgens. As a prohormone, however, DHEAS has no identifiable receptors and must be converted into testosterone and dihytestosterone (DHT) to express its androgenic attributes.[1,2]

DHEAS is converted into testosterone and DHT within cells of target tissues. This intracellular production is initiated by DHEAS-metabolizing enzymes (steroid sulfatases) to form DHEA, which is then converted to androstenedione, testosterone, and to DHT. DHT then interacts with the signal transduction systems of the androgen receptor.[1,2]

DHEAS concentrations in girls increase detectably beginning at seven to eight years of age and are associated with adrenarche: increasing pubic and axillary hair, emerging sexual desire, increasing strength and muscle mass, increasing bone mass, maturation of the immune system, and accelerated linear growth (see *Table 1*).[1,2]

DHEAS concentrations reach their peak in the 20s and 30s (see *Figure 1*). Production rates and circulating levels decline during the 40s and 50s. A clinical situation

1. *Buster J E, "Aging, androgens, and female sexual desire: can we restore what time takes away?"* Sexuality, Reproduction & Menopause *(2005):3(1): pp. 3–7.*
2. *Buster J E, Casson P R, "Where androgens come from, what controls them, and whether to replace them", in Lobo R A, ed,* Treatment of the Menopausal Woman: Basic and Clinical Aspects. 2nd ed. *(1999) Philadelphia, PA: Lippincott Williams & Wilkins; 1999: pp. 141–154.*

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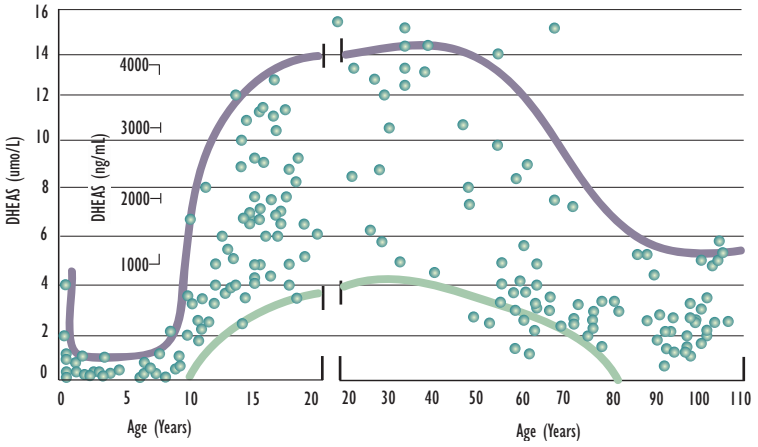
Figure 1: Circulating DHEAS in girls and women from birth through age 100



The graph is a composite of two studies. DHEAS concentrations, a direct reflection of DHEAS adrenal secretion, begin to increase in girls aged 7 to 8. Maximum lifetime concentrations are achieved during the decades of the 20s and 30s and begin a sustained decline through age 100. Outside bands enclose 95% of the data points.
Adapted from Babaloa AA, Ellis G: Clin Biochem 1985; 18(3): 184-9; and Ravaglia G, Forti P, Maioli F, et al. J Clin Endocrinol Metab 1996; 81(3):1173-8.

analogous to 'reverse adrenarche' emerges in which there is loss of pubic and axillary hair, decreasing sexual desire, loss of muscle mass and bone mass, immunosenescence, and declining stature.[1–4]

Just as there is an increase in zona reticularis mass at adrenarche, there is a decrease in zona reticularis mass and fragmentation of its cells with aging. The process closely resembles apoptosis. This decline in zona reticularis mass is associated with the falling production and declining concentrations of DHEAS that occur with advancing age.[3,4]

Testosterone during reproductive years evolves partly from peripheral intracellular conversion of DHEAS and partly from direct ovarian secretion that originates mostly from the dominant ovarian follicle of the month. Thus, a mid-cycle rise in testosterone concentrations occurs in conjunction with the luteinizing hormone (LH) surge, an event linked to increased mid-cycle sexual desire, which occurs at that time[1,2] (see *Figure 2*).

After menopause, the ovary evolves from a follicle-laden reproductive structure to an acyclic, androgen-secreting, stroma-dominant organ that shrinks to about half its original reproductive-age size. The post-menopausal ovary is believed to produce significant amounts of testosterone from its remnant stromal architecture. The chronically elevated levels of LH associated with menopausal years further augment this production.[1,2]

Table 1: Characteristics of Adrenarche and 'Reverse Adrenarche'

Adrenarche Ages 7 to 8	***Menopausal senescence or 'reverse adrenarche' Age 40 to 50***
Increasing sex hair	*Loss of sex hair*
Increasing libido	*Loss of libido*
Increasing bone density	*Loss of bone density*
Increasing stature	*Loss of stature*
Increasing muscle mass	*Loss of muscle mass*
Immune maturation	*Immunosenescence*

Modified from Buster.[1]

Testosterone concentrations do not drop abruptly after menopause in women with intact ovaries. While the mid-cycle testosterone rises, basal concentrations decline only gradually. Post-menopausal oophorectomy, however, is associated with a sharp drop in testosterone of approximately 40–50%. Not surprisingly, post-menopausal oophorectomy is associated with lost sexual desire.[1,2]

Declining androgens are associated with subtle symptoms that take years to evolve and can be difficult to recognize. Depletion of androgens is not lethal, but their decline may accelerate some processes traditionally associated with aging and mortality (i.e. the characteristics of reverse adrenarche that are summarized in *Table 1*).[1,2]

Sexual Apathy and Aging

Declining sexual desire with aging is well documented;[1,2] the author has reviewed it previously.[1,2] Female sexual desire is influenced by variables that include good general health, an available and attractive partner, freedom from psychotropic drugs (e.g. antidepressants), and a safe environment. Advancing age and the endocrinology of advancing age are but two aspects of a highly complex behavior.[1,2,5]

Sexual apathy appears to be one of the most prevalent female sexual problems across all age groups. Several surveys have compared women before menopause and after menopause:

3. *Hornsby P J, "Biosynthesis of DHEAS by the human adrenal cortex and its age-related decline",* Ann NY Acad Sci *(1995);774: pp. 29–46.*
4. *Labrie F, Belanger A, Sucan L et al., "Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging",* J Clin Endocrinol Metab *(1997);82: pp. 296–402.*
5. *Bachman G, Bancroft J, Braunstein G et al., "Female androgen insufficiency; the Princeton consensus statement on definition, classification, and assessment",* Fertil Steril *(2002);77: pp. 660–665.*

- a longitudinal study of women aged 45–55 found that multiple indices of sexual function, including desire, significantly declined from the late peri- to the post-menopausal years;[6]
- an interactive survey reported that 45% of post-menopausal women younger than 55 years of age indicated significant declines in sexual desire;[7] and
- multiple investigations show highly significant declines in sexual activity with advancing years.[8–10]

In addition to the effects of age, sexual desire declines in association with oophorectomy, menopausal estrogen therapy, treatment with corticosteroids, adrenal insufficiency and hypopituitarism, all of which result in diminished androgen availability. In a study assessing indices of sexual functioning between age-matched groups of women who had undergone hysterectomy with or without oophorectomy, the oophorectomized women experienced significant decreases in indices of sexual desire compared with those whose ovaries were not removed.[1,11–14]

Androgen Therapy Can Restore Sexual Desire

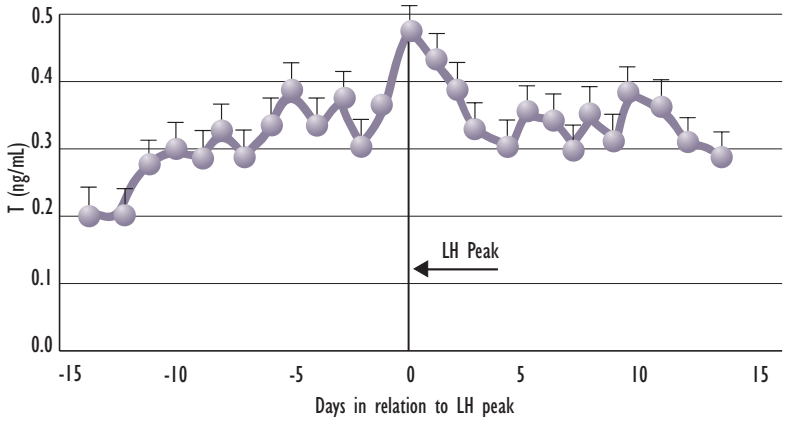
Androgens administered in pharmacologic doses can increase sexual desire, even in women who are chronically ill. Thus, many years ago, when androgens were administered as chemotherapy for advanced breast cancer, enhanced sexual desire was an unwelcome side effect. Even worse, virilization (e.g. male pattern baldness, deepening of the voice) was a common adverse reaction. The major problem over the years has been in devising systems that can deliver androgens at doses closely approximating the physiology of pre-menopausal androgen production.

Table 2: Testosterone Products

Product/manufacturer	When available
Intrinsa Patch/Proctor and Gamble	Failed initial approval 2004
MDTS spray/Vivus	Final studies FDA 2006;available 2007?
LibiGel gel/BioSante	Final studies; available 2007?
Androsorb cream/Novavax	Mid-phase studies; investigational
Estratest pill/Solvay	Approved for menopausal symptons; Sexual desire studies under way

Adapted from Seibel.[17] FDA = US Food and Drug Administration.

Figure 2: Mid-cycle rise in ovarian testosterone in a group of healthy women



Testosterone concentrations show a midcycle increase associated with the peri-ovulatory period.
LH, luteninizing hormone; T, testosterone.
Adapted from Abraham GE. Ovarian and adrenal contribution to peripheral androgens during the menstrual cycle. J Clin Endocrinol Metab 194;392(2):340-6.

Ideally, in otherwise healthy older women, the therapeutic goal is to restore sexual desire without virilizing side effects.[1]

A recent literature survey reveals at least six randomized single or double-blinded clinical trails showing significant increases in sexual desire with testosterone versus estrogen-only treatments.[14,15] In

6. *Dennerstein L, Dudley E, Burter H, "Are changes in sexual functioning during midlife due to aging or menopause?",* Fertil Steril *(2001);76: pp. 456–460.*
7. *Harris Interactive/PRIME PLUS/Red Hot Mamas, "Sexual Communeations Survey", Ridgefield, CN (2000).*
8. *National Council on Aging, "Healthy Sexuality and Vital Aging" Washington, DC (1998).*
9. *Association of Reproductive Health Professionals. Sexual Activity Survey, Washington, DC (1999).*
10. *Leiblum S R, Koochaki P E, Rosen R C, "Self-reported distress associated with decreased interest in sex as a function of age/menopausal status", presented at International Society for the Study of Women's Sexual Health, October 10–13, 2002; Vancouver, British Columbia.*
11. *Nathorst-Boos J, von Schoultz B, Carlstrom K, "Elective ovarian removal and estrogen replacement therapy – effects on sexual life, psychological well-being and androgen status",* J Psychosom Obstet Gynaecol *(1993);14: pp. 283–293.*
12. *Sarrel P, Dobay B, Wiita B, "Estrogen and estrogen-androgen replacement in postmenopausal women dissatisfied with estrogen-only therapy. Sexual behavior and neuroendocrine responses",* J Reprod Med *(1998); 43(10): pp. 847–856.*
13. *Arlt W, Callies F, Vlijmen JC et al., "Dehydroepiandrosterone replacement in women with adrenal insufficiency",* N Engl J Med *(1999);341: pp. 1,013–1,020.*
14. *Goldsmith C L, Maly J, Swanson S et al., "Esterified estrogens and methyltestosterone: effects on sexual interest and hormone profiles",* Obstet Gynecol *(2004);103 (Suppl): p. 63S.*

addition there are eight randomized, double-blind, placebo-controlled clinical trials demonstrating significant increases in sexual desire with testosterone treatment versus placebo.[16–18]

Two of these trials utilized a matrix patch (Intrinsa®, Proctor and Gamble) that delivered testosterone at 300µg per day. The subjects were all women who had undergone oophorectomy. This dose approximates normal production of testosterone in pre-menopausal women. At 300µg per day, there have been consistent increases in sexual desire with surprisingly few adverse effects. Of particular note, the psychological instruments used in the six placebo-controlled trials where devised specially to measure attributes of sexual desire.[15,16] Two of the studies involved over 1,100 women but were limited to 24 weeks, so that long-term effectiveness and side effects beyond that timeframe are not known.[15,16] In December 2004, a US Food and Drug Administration (FDA) advisory committee, concerned that the increase in sexual desire was too modest and that long-term effects were not yet adequately documented, recommended against approval of Instrinsa®. The FDA followed its advice, and Intrinsa® is not available.[19]

The FDA has Declined All Androgen Treatments

The FDA has not approved any androgen treatment for decreased sexual desire. Given that some 145,000 women have received prescriptions for testosterone gel (for men at 10 times the dose) and that at least 20% of testosterone gel sales are to women, there is considerable pressure on the agency to re-examine this issue.[19] In the meantime, physicians have other options. Many androgen preparations are prescribed off-label or are self-administered. These include topical gels, creams, vaginal gels, subcutaneous implants, and testosterone patches (developed for men), intramuscular (IM) injections, sublingual tablets, oral methyltestosterone, and oral DHEA.

Three off-label androgen regimens include:

- Methyltestosterone, 1.25mg per day, given with oral conjugated estrogens, 0.625mg, as Estratest® (Solvay). In a randomized, controlled trial of 16 weeks, Estratest® significantly increased sexual desire.[17]
- Testosterone in PLO gel is compounded by local pharmacies or can be obtained on the Internet. Preparations may contain variable and inconsistent doses and require intensive physician monitoring of blood testosterone levels to be administered safely.
- Testosterone implants containing 50–100mg can be placed surgically under the skin using local anesthesia. Each implant lasts about four months. These implants have been studied extensively in Australia where they have been demonstrated as effective in treating decreased sexual desire in limited clinical trials. They require extensive physician monitoring.[18]

Several androgen products, now undergoing clinical trials, are not clinically available (see *Table 2*).[19]

The Future

In the US, post-menopausal women in increasing numbers remain highly productive and influential. In response to their needs, hormone replacement treatments are becoming sophisticated and focused. There is clear documentation that androgen production declines in women as they age and that androgen production is linked to sexual desire. Furthermore, there is convincing evidence from well-designed and sizable clinical trials that restoration of androgens approximating physiology of reproductive years restores lost sexual desire to many. It is not yet known whether prolonged exposure to pre-menopausal androgens is safe. It is clear that, until the FDA approves, physicians and their patients will continue to use off-label, locally compounded products with unproven efficacy and undocumented safety. ■

A version of this artcile contaning additional graphics can be found in the Reference Section on the website supporting this briefing (www.touchendocrinedisease.com).

15. *Simon J A, Nachtigall L E, Davis S R et al., "Transdermal testosterone patch improves sexual activity and desire in surgically menopausal women",* Obstet Gynecol *(2004);103 (Suppl): p. 64S.*
16. *Buster J E, Kingsberg S A, Aguirre O et al, "Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial",* Obstet Gynecol *(2005);105 (5 Pt 1): pp. 944–952.*
17. *Seibel M, "Men, women and testosterone: why did the FDA fail Intrinsa?",* Sexuality, Reproduction & Menopause *(2005);3(1): pp. 1–2.*
18. *Lobo R A, Rosen R C, Yang H M et al., "Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire",* Fertil Steril *(2003);79: pp. 1,341–1,352.*
19. *Davis S R, McCloud P, Strauss B J, Burger H, "Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality",* Maturitas *(1995);21: pp. 227–236.*