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# Androgen therapy in women: for whom and when

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**Abstract** Androgens play a primary role in female physiopathology. The age-related reduction in the production of ovarian and adrenal androgens may significantly affect women's health. The decline of circulating androgens results from a combination of two events: reduced ovarian production and aged-related decline in adrenal androgen synthesis. The relative androgen deficiency in pre- and postmenopausal women may induce impairment of sexual function, libido, well-being, energy and may contribute to reduced cognitive functions. Whether androgen deficiency also affects cardiovascular or bone biology in women during reproductive aging is still controversial. Both in the central nervous system and peripheral tissues, there are multiple ways whereby androgens target their specific actions through a particular tropism of the brain areas that are involved in sexual function, behavior and cognition. Among circulating available androgens that are involved in several domains of sexual response, adrenal androgens seem to be related to some sexual symptoms as well as diminished cognitive function in postmenopausal women. The possibilities of treating low sexual desire/hypoactive sexual desire disorder are multifaceted and should include the combination of both pharmacological treatments able to maximize biological signals that drive the sexual response as well as individualized psychosocial therapies to overcome personal and relational difficulties. Transdermal testosterone has been proved to be effective but the use of additional treatment like oral or vaginal dehydroepiandrosterone is still controversial, despite many evidences support it. The decision to treat premenopausal or postmenopausal women with signs/symptoms of androgen insufficiency is mainly based on the clinical judgment, together with estrogens co-administration and following informed consent related to the unknown long-term risks.

**Keywords** Testosterone · DHEA/S · Reproductive aging

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## Introduction

During the last 40 years, drugs acting on androgen pathways have been widely used mainly for treatment for prostate cancer and other functional clinical situations in men and women.

The proper indication of androgens as a replacement treatment in women still leads to lack of certainty and reliability with a widespread skepticism among physicians. Despite some articles have shown conflicting results [1], androgen therapy seems to be a solution for those women with low level of androgen or who are clinically symptomatic of androgen deficiency.

The diagnosis of low androgen levels is not commonly reproducible; the normal range of androgen circulating levels in women is difficult to determine due to the intracellular conversion to active hormones and the difficulties in its measurement [2]. It is also the fear of secondary effects of androgen treatments and difficulties in assessing the adequate dosage to each patient that has limited their use to some clinical trials or just for specific indications. On the other hand, clinical trials are not always designed

for evaluating long-term therapy or secondary effects to achieve definitive conclusion. The present review briefly summarizes the physiology of androgen production as well as the available evidence of androgen treatment, and relative indications.

## Source and levels of androgens

In premenopausal women, the ovaries produce approximately 25 % of testosterone, 25 % by the adrenals and the remainder is from local production in tissues such as adipose and muscle, using precursors produced by the ovaries and adrenals. After menopause, the ovaries produce 50 % and adrenal production drops to 10 %. The biological activity of androgens depends on a number of factors; the ability to deliver the androgen via the circulation to target tissues must occur, the androgen must be able to bind to its receptors in target tissues, downstream regulation must occur after binding and the production and clearance rates of the androgen must be regulated. Transformation of the adrenal/ovarian precursor steroids dehydroepiandrosterone-sulfate (DHEA-S) and dehydroepiandrosterone (DHEA) into androgens and/or estrogens in peripheral target tissues depends upon the level of expression of the various steroidogenic and metabolizing enzymes in each cell of these tissues. This sector of endocrinology that focuses on the intracellular hormone formation and action has been called intracrinology. This term was coined [3] to describe the synthesis of active steroids in peripheral target tissues where the action is exerted in the same cells where synthesis takes place without release of the active steroids in the extracellular space and general circulation. In women, the role of the adrenal precursors DHEA-S, DHEA and androstenedione (A) in the peripheral formation of testosterone (T) and estrogens is even more important than in men. In fact, in men, androgen secretion by the testes continues at a high level throughout life while, in women, estrogen secretion by the ovaries completely ceases at menopause, thus leaving the adrenals as the only source of sex steroids. In fact, the best estimate is that the intracrine formation of estrogens in peripheral tissues in women accounts for 75 % of all estrogens before menopause, and close to 100 % after menopause [4]. In addition to estradiol (E2), another important estrogen is androst-5-ene-3β,17β-diol (5-diol). This steroid of adrenal origin has, in fact, been shown to exert direct estrogenic effects in both normal and malignant estrogen-sensitive tissues at concentrations found in the circulation of normal adult women (mammary gland, endometrium, adipose tissue, cardiovascular system, bone, brain and skin are the tissues in which intracrinology has been demonstrated).

The menopausal ovary can be considered an androgen-secreting organ, although, producing a lower rate of androgen than in the fertile women. In postmenopausal ovarian vein, T concentrations are higher than those in peripheral blood [5], and in oophorectomized postmenopausal women, both circulating levels of T [6] and A [7] decrease 50 and 30 %, respectively, when compared with women with normal menopause[8]. However, a significant reduction in T circulating levels occurs in premenopausal women when compared with fertile women: circulating T levels in women at forties are 50 % of those of women at twenties. In addition, circulating Δ5-androgens fall linearly with age from the 3rd decade of life, independently of menopausal transition. After 70 years of age DHEA(S) levels are 20 % or less of the maximum plasma concentrations, while cortisol levels remain unchanged. In fact, it has been hypothesized that during the aging process, the reduction of 17,20 desmolase activity, the enzyme that rules the biosynthesis of the Δ5-adrenal pathway, may induce modifications in DHEA(S) synthesis [9, 10]. The decline in Δ5-androgens and the parallel increase in cortisol/DHEA(S) ratio has been reported to be in part responsible of the physiological and/or pathophysiological age-related changes [11, 12]. It can be suggested that the decline of circulating androgens results from a combination of two events: ovarian failure plus aged-related decline in adrenal androgens. However, the decline in circulating T, A and in particular in DHEA(S) levels begin in the decades that precedes the menopause and could be detected in the premenopausal and/or perimenopausal years. Estrone produced by the peripheral conversion of A, becomes the most important estrogen in postmenopause. However, only 5 % of the formed estrone is converted to E2 during menopause through the action of the 3 beta-hydroxy steroid dehydrogenase enzyme [13]. The amount of estrone generated is a good indicator of A metabolism [14] in postmenopausal women.

## Female androgen deficiency: does it exist?

The concept of "female androgen insufficiency disorder" was used for the first time in 2001 [15]. Androgen deficiency can occur in women at any age, either during their reproductive life or in menopause. Clinical signs and symptoms of low androgen exposure seem to be most pronounced in the postmenopausal period.

The dominating effects of estrogen in women, particularly on mood and sense of well-being, can mask the impact of decreased androgen exposure in premenopausal women. Those clinical manifestations of chronic and reduced androgen exposure can be prolonged in onset over several years and thus can easily be confused with general signs and symptoms of normal aging.

During the last decades, three guidelines have been published setting the position of three societies about androgen therapy in women; the first in 2005 by the North American Menopause Society [16], the second a year later by The Endocrine Society [17] and the last in 2010 by The British Society for Sexual Medicine (BSSM) for the assessment of testosterone deficiency in both women and men [18].

Female androgen insufficiency syndrome includes a diminished sense of well-being, dysphoric mood, persistent, unexplained fatigue, irritability, insomnia, and clinical manifestations related to sexuality (low libido and desire). Other potential signs or symptoms attributable to low androgen levels are vasomotor instability or decreased vaginal lubrication, bone loss, decreased muscle strength, and changes in cognition or memory. It is imperative that psychiatric illnesses, causes of chronic fatigue (as could be major depression or hypothyroidism), and estrogens deficiency must be ruled out.

## Androgen deficiency and sexual dysfunction in women

Among the causes underlying sexual impairments, the role of androgens in women's sexual functioning has been an issue of debate for a long time. Multiple randomized, double-blind, placebo-controlled treatment trials have demonstrated that T improves libido and other sexual functions significantly more than placebo does. But data linking low androgen levels to low desire are still inconclusive: no T level has been found to be predictive for low female sexual function, according to the findings of studies and given the difficulties in measuring androgens properly and the multitude of physiological, psychological, social and lifestyle factors that may be involved in these disorders [19].

The International Consensus Development Conference on Female Sexual Dysfunction [20] created four categories of sexual impairments in women. Among them, sexual desire disorders include the hypoactive sexual desire disorder (HSDD) that is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision as persistent or recurrent deficiency or absence of sexual fantasies and thoughts, and/or desire for, or receptivity to, sexual activity, which causes personal distress or interpersonal difficulties and is not caused by a medical condition or drug. HSDD is the most common cause of female sexual dysfunction [21].

The clinician taking into account, factors that affect sexual functioning, such as age and context of the patient's life makes the judgment of "deficiency or absence". From those criteria, it is induced the wide subjective diagnostic judgment the physician can make: it is the same description for both men and women, lack of desire at the outset of sexual engagement is common for sexually content women and sexual thoughts are infrequent in many women without sexual complaints.

There are some small studies that support the association between testosterone and libido: Turna et al. [22] found significant differences between the women with low libido and the controls in total T, free T and DHEAS levels and full-scale Female Sexual Function Index score in pre- and postmenopausal women. Decreased total T, free T and DHEAS levels also correlated positively with desire, arousal, lubrication and orgasm scores. Guay et al. [23] described lower adrenal androgen precursors and T in women with complaints of sexual dysfunction than in age-matched control women without sexual problems.

Nonetheless, the correlation between testosterone levels and sexual function has been reported to be minimal in the Study of Women's Health Across the Nation (SWAN study) [24] or not existing in other studies [25, 26].

For long time, sexual problems in women have been treated with high doses of T or methyl-testosterone rising supraphysiological androgen levels with clinical improvements and also important side effects. From 1990, other options specially design for women have been searched: T addition to the classical estrogen replacement therapy, or new low-dose options including transdermal or vaginal ways of androgen administration.

Some recent studies in HSDD women showed improvement of sexual symptoms using low-dose androgen therapy (APHRODITE Study Team) [27]. In a randomized, double-blind, placebo-controlled study, 814 menopause women received transdermal T 300 μg/day. In the same group of women, blood concentrations of free and bioavailable T remained within reference range for premenopause women as published by Davison [2]. Panay et al. [28], in the ADORE study, a 6-month placebo-controlled, double-blind, multicenter study, 272 natural menopause women treated with 300 μg/day of transdermal testosterone reported sexual improvements.

Braunstein [29] compared 447 surgical menopause women with HSDD who were under estrogen therapy, the efficacy of three different doses of transdermal T (150, 300, 450 μg/day) and placebo for 24 weeks. The 300 μg/day group had significantly greater increases from baseline in sexual desire and frequency when compared with placebo. The 150 μg/day group did not show any significant treatment effect. Interestingly, the 450 μg/day was not statistically different from the 300 μg/day. Treatment groups were similar in the proportion of women with androgenic adverse events. Similar results have been found in premenopausal women with T cream at 10 mg/day for 12 weeks [30] and with T spray at the 90 μg doses [31].

Endocrine Society makes recommendation against the generalized use of T, and the North American Menopause

Society published, a year before, on its guideline [16] that although data are limited, there is consistent evidence that in postmenopausal women with sexual concerns, adding either oral or non-oral T to estrogen therapy results in a positive effect on sexual function, primarily an increase in sexual desire.

These discrepancies may be due to a different concept of androgen insufficiency and different emphasis in risks–benefits from each indication and results. Since the position statements were formulated, transdermal testosterone has been approved and is available in several countries [32].

The BSSM suggested [17] that treatment of women with sexual desire and arousal problems should be individually tailored and may include psychosexual therapy, estrogen, T or tibolone.

## Androgen deficiency in particular clinical conditions

There is a recognizable constellation of signs and symptoms in women due to androgen deficiency in particular clinical conditions such as hypothalamic-pituitary abnormalities, adrenal insufficiency, premature ovarian failure, iatrogenic menopause (chemotherapy, radiation, bilateral oophorectomy), anorexia nervosa, HIV-wasting disease, and, glucocorticoid therapy.

In addition, conventional estrogen–progestin intakes regimens, affecting ovarian steroidogenesis, as oral contraceptives (OCs), reduce endogenous androgens production. Moreover, in fertile and in postmenopausal women, the use of oral estrogens results in an increase in sex hormone binding globulin levels, which lower the free T levels and may precipitate loss of libido [33]. Another mechanism responsible of hypoandrogenemia in healthy women consuming OCs is the decrease of DHEAS and DHEA levels [34, 35].

However, in many cases there are no clear biochemical criteria, the hallmarks for the diagnosis of androgen deficiency are a decrease in libido and sense of well-being accompanied by an increase in unexplained fatigue. Other associated signs include osteopenia or osteoporosis, a decrease in lean body mass and loss of pubic hair, dysphoria, and other mood disorders.

The approach to diagnosing androgen insufficiency syndrome is one of exclusion. Other disorders associated with a low libido to be considered include depression, relationship issues, medications, and medical illness. In the presence of symptoms suggestive of androgen deficiency, measurements of free T or free T index can be obtained. If T is within the upper 2/3 of the normal range, insufficiency is unlikely to be the cause of the signs and symptoms occurring. However, as the majority of postmenopausal women fulfilling the criteria for HSDD have low T levels, measurement is really not cost-effective. Therefore, a trial of T therapy may be considered also without obtaining measurements.

### Anorexia nervosa

Anorexia nervosa (AN) is a psychiatric disorder that includes metabolic and hormonal disturbances characterized by central hypogonadism, hypercortisolemia, hypotiroidism, and is complicated by severe bone loss (osteopenia 92 % and osteoporosis 38 %), cognitive impairment, and a high prevalence of mood, and anxiety disorders including major depression.

Interestingly, these patients show reduced total and free T levels, with the lowest levels of free T observed in women with AN receiving OCs [36]. Several studies suggest that there is also dissociation between adrenal glucocorticoid and androgen secretion [37]. Data relative to DHEA(S) production in AN patients are contradictory, but definitely the consequence found is a reduced androgenemia that can lead to the low mood, anxiety, and to bone loss summed to the undernourishment they have.

There have been published some studies comparing the androgen treatment effect versus placebo in ameliorating those clinical manifestations in AN women: Miller demonstrated an increased bone formation associated with improved mood in depressed patients with AN, from severely depressed to moderately depressed with low-dose transdermal T administration (150 μg/day or, 300 μg/day) [38]. Interestingly, recently, low-dose T therapy with the use of risedronate (35 mg weekly) increases spinal bone mineral in young AN patients.

## DHEA therapy in postmenopausal women: the hormone of controversy

Over the past 10 years, hormone preparations of DHEA have been available over-the-counter and have been sold as the "fountain of youth". This has raised concerns about the real clinical efficacy and the possible effects of such uncontrolled and widespread hormonal self-administration and the lack of quality control in this increasingly rewarding business. Susan Davis and colleagues [39] recently reviewed the published literature on the effect of DHEA treatment in postmenopausal women. The authors only included randomized controlled trials that compared DHEA therapy with placebo in postmenopausal women not receiving other hormonal treatments. End-points analyzed were measures of sexual function, well-being and measures of safety such as lipids and carbohydrate metabolism. However, only nine well-designed studies are available in the literature analyzing sexual function and only seven

trials that address the issue of well-being, but they differ from dose and treatment time, age of women and, measured function. More findings are available on the effects on lipids levels and insulin sensitivity, but studies still lack of definitive evidence.

The authors conclude that there is a little convincing data to support the use of oral DHEA in healthy postmenopausal women to improve conditions evidenced with the aging process, such as reduced sexual function and reduced well-being.

This paper of Davis and colleagues renews the attention and the debate on one of the most attractive and controversial issue in the physiology of the aging process that is still far to be clearly defined by the scientific community.

The most relevant aspect, meriting attention is certainly the controversial finding among studies which investigate the correlation of endogenous DHEAS level, aging process or organ illness versus results coming from studies focusing on the effects of exogenous DHEAS administration on brain function, sexuality or cardiovascular health and metabolic syndrome.

Indeed, the marked age-related decline in serum DHEA and DHEA-S has suggested that a deficiency of these steroids may be causally related to the development of a series of diseases which are generally associated with aging. Postulated consequences of low DHEA include insulin resistance, obesity, cardiovascular disease, cancer, reduction of the immune defense as well as psychosocial problems such as depression and a general deterioration in the sensation of well-being and cognitive function [40].

There is also growing evidence in the literature that low DHEAS level, representing the most abundant sex steroids in plasma in humans (more than one thousand times higher than estradiol and testosterone level) negatively correlates with domains of sexual function in pre- and postmenopausal women [26] more than T levels do. Nonetheless, a DHEA-S cut-off level for defining androgen deficiency syndrome is not established. Similarly, in a cross-sectional study, higher endogenous DHEAS levels are independently and favorably associated with several measures of cognitive function and well-being [41].

As a consequence DHEA replacement may seem an attractive treatment opportunity. Nevertheless, the analyses of clinical outcomes are far to be conclusive and many issues should be still addressed. Despite DHEA preparation being available in the market since 1990s, there are very few definitive reports on the biological functions of this steroid, and it is still the case that its regulation is unclear and its mechanisms of action are largely yet to be established.

There is increasing evidence for DHEA acting in its own right through a dedicated, although as yet unidentified, receptor. The existence of such receptor for DHEA has been particularly investigated in the brain tissue and in vascular cells. In the brain DHEA is a neurosteroid that acts as modulators of neurotransmitter receptors, such as gamma-aminobutyric-acid-type A, NMDA, and sigma-1 receptors. In vitro and in vivo documented effects involve neuroprotection, neurite growth, neurogenesis and neuronal survival, apoptosis, catecholamine synthesis and secretion, as well as anti-oxidant, anti-inflammatory, and anti-glucocorticoid effects [42]. In the vessels, DHEA binds with high affinity to the endothelial cell membrane, and structurally related steroids do not displace it. Binding of DHEA to the cell membrane is coupled to recruitment of G proteins such as G{alpha}i2 and G{alpha}i3 that mediate the rapid activation of intracellular signaling cascades [43].

Although there is still debate on DHEA receptor, these findings corroborate the evidence that DHEA is not just a pre-hormone of the adrenals, but rather a hormone in its own right, and that it modulates a series of biological processes' with a remarkable tropism for the central nervous system.

Clinically, the spectrum of women that would benefit from DHEA therapy is not clearly defined as well as the dosage of hormone treatment. Whether DHEA therapy could be prescribed as a general anti-aging therapy or could be an alternative treatment for women suffering from androgen deficiency syndrome, remains uncertain across studies. In particular, among symptomatic women, the spectrum of DHEA responding symptoms requires further investigation, to define the type of sexual symptoms (e.g. decreased sexual function or HSDD) and the degree of mood/cognitive symptoms that could be responsive to hormonal treatment. Similarly, the definition of criteria for the choice of DHEA starting dosage to be prescribed in postmenopausal women needs further investigation: extent of symptoms, baseline DHEA(S) plasma levels, concomitant estrogen therapy or the combination of all the previous, should be considered.

Plasma DHEA(S) levels at baseline and during treatment merit attention given that a cut-off value for DHEA(S) deficiency is not yet defined and plasma level might not represent the rate of tissue conversion into estrogens or delta-4 androgens. This fact is also coupled with the route of administration of DHEA given that, oral, vaginal and parental administrations seem to induce different steroid concentration in the plasma with different clinical consequences and applications [44, 45].

All these findings may have far-reaching implications in the debate about the role of DHEA(S) in female aging process and might reconcile discordant findings from basic science and clinical studies. The lack of definitive evidence of biological mechanisms and the presence of only few studies that address these emerging issues of DHEA therapy in postmenopausal women might encourage a new critical analysis of the available literature, evidencing

current limits and incongruities. Concurrently, the design of new clinical trials, specifically planned on the biology of symptomatic postmenopausal women and designed for the translation of basic science into clinical practice, is now a required step to move foreword in the scientific debate of DHEA.

**Conflict of interest** None.

## References


1. Davis SR, Panjari M, Stanczyk FZ (2011) DHEA replacement for postmenopausal women. J Clin Endocrinol Metab 96:1642–1653
2. Davison SL, Bell R, Donath S, Montalto JG, Davis SR (2005) Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab 90:3847–3853
3. Labrie C, Bélanger A, Labrie F (1988) Androgenic activity of dehydroepiandrosterone and androstenedione in the rat ventral prostate. Endocrinology 123:1412–1417
4. Labrie F (2003) Extragonadal synthesis of sex steroids: intracrinology. Ann Endocrinol (Paris) 64:95–107
5. Judd HL, Judd GE, Lucas WE, Yen SS (1974) Endocrine function of the postmenopausal ovary concentration of androgens and estrogens in ovarian and peripheral vein blood. J Clin Endocrinol Metab 39:1020–1024
6. Rabinovici J, Rothman P, Monroe SE, Nerenberg C, Jaffe RB (1992) Endocrine effects and pharmacokinetic characteristics of a potent new GnRH antagonist (Ganirelix) with minimal histamine-releasing properties: studies in postmenopausal women. J Endocrinol Metab 75:1220–1225
7. Judd HL, Lucas WE, Yen SS (1974) Effect of oophorectomy on circulating testosterone and androstenedione levels in patients with endometrial cancer. Am J Obstet Gynecol 118:793–798
8. Couzinet B, Meduri G, Lecce MG, Young J, Brailly S, Loosfelt H et al (2001) The postmenopausal ovary is not a major androgen-producing gland. J Clin Endocrinol Metab 86:5060–5066
9. Liu CH, Laughlin GA, Fischer UG, Yen SS (1990) Marked attenuation of ultradian and circadian rhythms of dehydroepiandrosterone in postmenopausal women: evidence for a reduced 17,20 desmolase enzymatic activity. J Clin Endocrinol Metab 71:900–907
10. Couch RM, Muller J, Winter JS (1986) Regulation of the activities of 17-hydroxylase and 17,20-desmolase in the human adrenal cortex: kinetic analysis and inhibition by endogenous steroids. J Clin Endocrinol Metab 63:613–618
11. Mortola JF, Yen SS (1990) The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. J Clin Endocrinol Metab 71:696–704
12. Morales AJ, Nolan JJ, Nelson JC, Yen SS (1994) Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Endocrinol Metab 78:1360–1367
13. Luu-The V, Dufort I, Pelletier G, Labrie F (2001) Type 5 17 beta-hydroxysteroid dehydrogenase: its role in the formation of androgens in women. Mol Cell Endocrinol 171:77–82
14. Al-Azzawia F, Palacios S (2009) Hormonal changes during menopause. Maturitas 63:135–137
15. Bachmann G, Bancroft J, Braunstein G, Burger H, Davis S, Dennerstein L et al (2002) Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. Fertil Steril 77:660–665
16. Shifren JL, Davis SR, Dennerstein L, Heiman JR, Lobo RA, Simon JA (2005) The role of testosterone therapy in postmenopausal women: position statement of the North American Menopause Society. Menopause 12:497–511
17. Wierman ME, Basson R, Davis SR, Khosla S, Miller KK, Rosner W et al (2006) Androgen therapy in women: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 91:3696–3710
18. Wylie K, Rees M, Hackett G, Anderson R, Bouloux PM, Cust M et al (2010) Androgens, health and sexuality in women and men. Review. Maturitas 67:275–289
19. Schwenkhagena A, Studdb J (2009) Role of testosterone in the treatment of hypoactive sexual desire disorder. Maturitas 63:152–159
20. Basson R, Berman J, Burnett A, Derogatis L, Ferguson D, Fourcroy J et al (2000) Report of the International Consensus Development Conference on Female Sexual Dysfunction: definitions and classifications. J Urol 163:888–893
21. Braunstein GD (2006) Androgen insufficiency in women. Growth Horm IGF Res 16 (Suppl A): S109–17
22. Turna B, Apaydin E, Semerci B, Altay B, Civili N, Nazli O (2005) Women with low libido: correlation of decreased androgen levels with female sexual function index. Int J Impot Res 17:148–153
23. Guay A, Jacobson J, Munarriz R, Traish A, Talakoub L, Quirk F et al (2004) Serum androgen levels in healthy premenopausal women with and without sexual dysfunction: part B. Reduced serum androgen levels in healthy premenopausal women with complaints of sexual dysfunction. Int J Impot Res 16:121–129
24. Santoro N, Torrens J, Crawford S, Allsworth JE, Finkelstein JS, Gold EB, Korenman S et al (2005) Correlates of circulating androgens in mid-life women: the study of women's health across the nation. J Clin Endocrinol Metab 90:4836–4845
25. Basson R, Brotto LA, Petkau AJ, Labrie F (2010) Role of androgens in women's sexual dysfunction. Menopause 17:962–971
26. Davis SR, Davison SL, Donath S, Bell RJ (2005) Circulating androgen levels and self-reported sexual function in women. JAMA 294:91–96
27. Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M et al (2008) Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med 359:2005–2017
28. Panay N, Al-Azzawi F, Bouchard C, Davis SR, Eden J, Lodhi I et al (2010) Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. Climacteric 13:121–131
29. Braunstein GD, Sundwall DA, Katz M, Shifren JL, Buster JE, Simon JA et al (2005) Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Arch Intern Med 165:1582–1589
30. Goldstat R, Briganti E, Tran J et al (2003) Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. Menopause 10:390–398
31. Davis S, Papalia MA, Norman RJ, O'Neill S, Redelman M, Williamson M et al (2008) Safety and efficacy of a testosterone metered-dose transdermal spray for treating decreased sexual satisfaction in premenopausal women: a randomized trial. Ann Intern Med 148:569–577
32. Braunstein GD (2007) The Endocrine Society Clinical Practice Guideline and The North American Menopause Society position statement on androgen therapy in women: another one of Yogi's forks. J Clin Endocrinol Metab 92:4091–4093
33. Lobo RA (2001) Androgens in postmenopausal women: production, possible role, and replacement options. Obstet Gynecol Surv 56:361–376
34. Moutos D, Smith S, Zacur H (1995) The effect of monophasic combinations of ethinyl estradiol and norethindrone on gonadotropins, androgens and sex hormone binding globulin: a randomized trial. Contraception 52:105–109

35. Carlstrom K, Karlsson R, Von Schoultz B (2002) Diurnal rhythm and effects of oral contraceptives on serum dehydroepiandrosterone sulfate (DHEAS) are related to alterations in serum albumin rather than to changes in adrenocortical steroid secretion. Scand J Clin Lab Invest 62:361–368
36. Miller KK, Lawson EA, Mathur V, Wexler TL, Meenaghan E, Misra M et al (2007) Androgens in women with anorexia nervosa and normal-weight women with hypothalamic amenorrhea. J Clin Endocrinol Metab 92:1334–1339
37. Lawson EA, Misra M, Meenaghan E, Rosenblum L, Donoho DA, Herzog D (2009) Adrenal glucocorticoid and androgen precursor dissociation in anorexia nervosa. J Clin Endocrinol Metab 94:1367–1371
38. Miller KK, Grieco KA, Klibanski A (2005) Testosterone administration in women with anorexia nervosa. J Clin Endocrinol Metab 90:1428–1433
39. Panjari M, Davis SR (2010) DHEA for postmenopausal women: a review of the evidence. Maturitas 66:172–179
40. Labrie F, Luu-The V, Bélanger A, Lin SX, Simard J, Pelletier G et al (2005) Is dehydroepiandrosterone a hormone? J Endocrinol 187:169–196
41. Davis SR, Shah SM, McKenzie DP, Kulkarni J, Davison SL, Bell RJ (2008) Dehydroepiandrosterone sulfate levels are associated with more favorable cognitive function in women. J Clin Endocrinol Metab 93:801–808
42. Genazzani AR, Pluchino N, Begliuomini S, Stomati M, Bernardi F, Pieri M et al (2006) Long-term low-dose oral administration of dehydroepiandrosterone modulates adrenal response to adrenocorticotropic hormone in early and late postmenopausal women. Gynecol Endocrinol 22:627–635
43. Simoncini T, Mannella P, Fornari L, Varone G, Caruso A, Genazzani AR (2003) Dehydroepiandrosterone modulates endothelial nitric oxide synthesis via direct genomic and nongenomic mechanisms. Endocrinology 144:3449–3455
44. Labrie F, Archer D, Bouchard C, Fortier M, Cusan L, Gomez JL et al (2009) Serum steroid levels during 12-weeks intravaginal dehydroepiandrosterone administration. Menopause 16:897–906
45. Pluchino N, Ninni F, Stomati M, Freschi L, Casarosa E, Valentino V et al (2008) One-year therapy with 10 mg/day DHEA alone or in combination with HRT in postmenopausal women: effects on hormonal milieu. Maturitas 20:293–303