

Female Androgen Insufficiency

Gloria Bachmann, MD*, Deepa Oza, MBBS, MPH

University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Hospital Medical School, Women's Health Institute, 125 Patterson Street, 1CAB-2104, New Brunswick, NJ 08903-2601, USA

The diagnosis of female androgen insufficiency (FAI) is difficult to objectively quantify because of the lack of a sensitive assay that detects low levels of androgens. Most assays are more specific in measuring hyperandrogenic states than they are in measuring hypoandrogenic states. Because of the multifactorial etiology of androgen insufficiency in women, there is no single, universally accepted management algorithm for women diagnosed with this entity. Androgen therapies currently available, whether oral, transdermal (patch, cream, or gel), or intramuscular, are Federal Drug Administration (FDA) approved only for men, not for women. Testosterone treatments for women when prescribed are done so off label, using products that are FDA approved for men. The only formulation available in the United States for women, an oral estrogen/methyl testosterone formulation, although used for FAI is indicated for postmenopausal women on estrogen therapy who continue to have vasomotor symptoms, and not for sexual dysfunction. Further studies addressing androgen insufficiency in women, including how to objectively confirm the diagnosis and what are the optional treatment interventions, are a research priority.

Female androgen insufficiency

Woman's sexual health, despite its overall importance, has been ignored by the clinical and research community. In the arena of androgens and androgen therapy in women, there has been an even greater dearth of clinical trials work. Scientific research has focused more on the role of androgens in men, because androgen production is much higher in men than in women, and the impact of hypoandrogenism in men can be more objectively assessed

* Corresponding author.

E-mail address: gloria.bachmann@umdnj.edu (G. Bachmann).

as compared with women. Data on the effects of androgen decline in women are scant; most research on the role of androgens in women has focused on hyperandrogenic states, such as polycystic ovarian syndrome. Recently, multiple studies addressing female sexual disorders, especially FAI, have reported that androgen loss does occur in women, especially in women after oophorectomy surgery, that there are noted sexual dysfunctions associated with their loss, and that androgen therapy is effective in reversing many of the sexual issues that occur from androgen loss, including amelioration or elimination of the loss of sexual desire and sexual arousal complaints.

Androgens, produced by the ovary and adrenals, are the major sex steroids in men and women, and in both sexes they are responsible for sexually motivational activities. For women, because the ovaries are one of the major producers of androgens, a decline in androgen synthesis often occurs with menopause, such that women lose androgens and estrogens at this stage in their life cycle. The loss of estrogen superimposed on the loss of androgens, especially testosterone, leads to an increase in sexual dysfunction characterized by loss of libido, insertional dyspareunia, and a diminution in sexual desire. In addition to sexual complaints, women often complain of adverse mood changes, muscle wasting, and fatigue that can also be attributable to the loss of androgen and estrogen.

Androgen production and metabolism

In the female, the ovaries and adrenals both play a major role in the biosynthesis of androgens. Of all androgens produced by the female, approximately 20% to 25% come from ovarian sources, 50% from adrenal sources, and 25% to 30% by peripheral conversion in adipose tissue, muscle, and skin. The stimulation for androgen production is regulated by the pituitary gland through luteinizing hormone (LH) for ovaries and adrenocorticotropic hormone (ACTH) for adrenals. The adrenals are able to produce the androgenic steroids dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione, testosterone (T), and dihydروtestosterone (DHT), whereas the ovaries can produce all of these androgens except DHEAS.

Testosterone is the most significant biologically active androgen in males and in females. It is also a precursor of dehydroepiandrosterone. Ovaries and adrenals produce 50% of testosterone, whereas 50% is contributed by peripheral conversion of androstenedione into testosterone. Androgens are the major precursors for estrogen production also; this production mainly occurs by aromatization of androstenedione to estrone and testosterone to estradiol. Androgens once released into the peripheral circulation bind mainly to sex steroid binding globulin (SHBG) and albumin to some extent; the levels of free or bioavailable androgens are the components of the circulating androgens that can bind to androgen receptors. The quantity of bioavailable androgens, the degree of their binding with SHBG, their affinity to receptors and their

biologic potency, and the degree of peripheral conversion to estrogens and other androgens influence androgen actions in the body [1]. In the unbound state, androgens act not only on genital structures, but also on multiple sites, including the central nervous system, hypothalamus, bone, breast, pilosebaceous unit of skin, skeletal muscle, and adipose tissue.

Variations in SHBG levels directly affect concentrations of free or bioavailable androgens, especially testosterone, which has the highest affinity to SHBG. The administration of exogenous oral estrogens increases the levels of SHBG and consequently decreases the levels of bioavailable androgens, which may in some women create an environment of relative androgen deficiency. SHBG levels also tend to increase with pregnancy, advancing age, cirrhosis, and anorexia nervosa. Drugs that cause an increase in SHBG levels are oral estrogens, such as those in oral contraceptives, excessive thyroid hormone, and some antiepileptic drugs.

Etiology of female androgen insufficiency

There seem to be five etiologic categories of FAI that include ovarian, adrenal, hypothalamic-pituitary, drug-related, and idiopathic. Some diseases like HIV/AIDS, anorexia nervosa, rheumatoid arthritis, systemic lupus erythematosus, and depression also cause decrease in androgen levels and sexual dysfunction in women. The most common cause of androgen deficiency is surgical removal of the ovaries and aging. Other known causes of FAI include any etiology causing ovarian dysfunction, such as natural menopause, chemotherapy or radiotherapy, hysterectomy, adrenal failure, hypopituitarism, autoimmune diseases, and anti-androgen therapy [2].

Women who have FAI often present with nonspecific complaints of malaise and fatigue, but can also present with a female sexual dysfunction (FSD). After analyzing multiple cross-sectional studies performed on women at different ages, Braunstein and colleagues found a positive correlation between testosterone levels and sexual arousal, initiation, desire, and frequency of intercourse and sexual gratification [3]. Any condition that leads to a decrease in circulating levels of bioavailable androgens therefore may have a negative impact on sexual wellbeing.

Pathophysiology of androgen production

Davison and colleagues [4] reported a decline in free and total testosterone levels in previously oophorectomized women as compared with normal women after menopause, which infers that surgically menopausal women are at greater risk for FAI. Goldstein and colleagues [5] investigated effects of oophorectomy in laboratory animals. These investigators looked at estrogen effect on urogenital health. Oophorectomy markedly decreased vaginal lubrication and vaginal blood flow, whereas administration of estrogens in oophorectomized animals restored vaginal blood flow and lubrication. They concluded that ovaries play a key role in female sexual health by

maintaining vaginal blood flow and lubrication, thereby decreasing vaginal atrophy and consequent dyspareunia and sexual dissatisfaction.

Miller and colleagues [6] studied the role of decreased androgen levels in women who had hypopituitarism with central hypogonadism, as compared with estrogen-depleted or estrogen-replete control subjects. Female androgen levels were consistently lower in women who had hypopituitarism than in normal women. The effects of estrogen therapy in premenopausal and postmenopausal women who had hypopituitarism were different as compared with women without hypopituitarism. That is, androgen levels were lower in women who had hypopituitarism even after estrogen therapy as compared with postmenopausal women receiving the same treatment, indicating the importance of pituitary regulation in androgen production.

It seems that female androgen production requires coordination of the ovaries, the adrenals, and the pituitary, and that adequate androgen production ultimately requires an intact hormonal axis.

Changes in androgen levels with age and other medical conditions

Androgens are produced throughout the female reproductive life but have fewer cyclic changes during the reproductive years as compared with estrogens. Androgen production, however, does have a circadian pattern, with production being higher during morning; androgen levels are also associated with the phases of the menstrual cycle. During an ovulatory menstruation cycle, androgen levels show a midcycle increase and then gradually decrease toward the premenstrual phase of the cycle. After the reproductive years, androgen levels are also noted to decline, with the decline beginning as early as the midlife years.

Davison and colleagues [4] conducted a randomized cross-sectional study of 1423 women in Australia to study the effects of natural versus surgical menopause on androgen levels. Steroids assessed in the study were total and free testosterone, dehydroepiandrosterone, and androstenedione. These investigators noted a significant decline in androgen levels with age that was not accompanied by a corresponding change in SHBG levels. Of great interest, the most significant decline in androgen levels was seen in early reproductive years, with subsequent flattening in mid life. During the later years, in comparison with a decline in estrogen levels, there was a small increase in androgen levels in the later years. Menopause in itself did not have a tremendous impact on androgen levels as compared with the marked decline in estrogen levels. Regarding the cyclic changes previously reported occurring during the various phases of the menstrual cycle with an increase noted in androgen levels during mid cycle, these were not observed. Rather, they observed a loss of midcycle increase in androgens that has been associated as occurring in normal young menstruating females. As expected, in oophorectomized women, the levels of testosterone and free testosterone were lower than non-oophorectomized women after menopause, but levels

of DHEA and androstenedione did not seem to be affected. After menopause, androgen production in the ovary is stimulated by persistently elevated levels of luteinizing hormone (LH), which may account for less change in androgen levels as compared with estrogen levels in postmenopausal women. In contrast with the previous studies, this study suggested an increase in SHBG levels after menopause in normal and in oophorectomized women. The effects of uterine excision and bilateral tubal ligation had no significant effect on androgen levels in the women studied. Levels of circulating androgens in this study and the values recorded, however, could be explained by alterations in the adrenal glands and may not reflect a universal ovarian etiology. Further research to determine underlying mechanisms of androgen production and levels throughout the female life cycle is advisable.

Signs and symptoms of female androgen insufficiency

There are many signs and symptoms of FAI, which include muscle wasting, mood changes, fatigue, loss of sexual motivation, and decrease in sexual desire. The most common cause of androgen insufficiency is aging, and it is also associated with a decrease in estrogen levels. Changes in levels of estrogens and androgens seen during menopause and aging have some psychologic and physical effects that include many diverse signs and symptoms. Along with androgens, estrogens also have effects on female sexual health, and their effects are difficult to analyze separately. Not only effects, but their circulation and production are also interrelated. It has been reported that estrogen depletion often results in dyspareunia, sleep disturbances, mood swings, hot flushes, vaginal drying, and atrophy.

Cameron and colleagues [7] suggested some signs and symptoms of FAI, including loss of libido, flattened mood, lack of sexual desire and motivation, and mood changes. Signs of FAI include thinning of pubic hair, osteoporosis, and decreased body mass.

To date, a clinical cluster of FAI recognized by most investigators includes loss of libido, lack of sexual desire and motivation, mood changes, and diminished wellbeing. These symptoms and signs are not found solely in androgen insufficiency, however; they are also seen in many other psychologic and physical conditions other than androgen deficiency. Factors like relationship issues, partner technique, medication, and general health also contribute to sexual health. Because of the multifactorial etiology of FAI, it is difficult to define its clinical scenario.

Diagnosis of female androgen insufficiency

Because female sexuality also has emotional and mental components, the diagnosis and scales to define degree of dysfunction remain obscure, leading to difficulty in interpretation of severity of the problem. Some of the important emotional and mental factors contributing to female sexual wellbeing are anxiety, stress, substance abuse, partner performance, and quality of

relationship. So far, adrenal gland dysfunctions have been considered as the most common cause of FAI.

The diagnosis of FAI consists of a comprehensive sexual history, in some instances laboratory tests for testosterone levels, and exclusion of other medical conditions that may mimic androgen insufficiency. Regarding female sexual dysfunction, psychologic and intrapersonal issues should be ruled out before the diagnosis of FAI is made. Along these lines, a woman can have more than one cause of sexual dysfunction: an intrapersonal issue and FAI. It is therefore important to address all etiologies of sexual difficulty and not assume that one management strategy will lead to amelioration or elimination of the symptoms.

In 2001, the Princeton Consensus recommended diagnosis of FAI be made by history with possible confirmation by measuring serum hormone levels [8].

Decision-making algorithm for initiating androgen therapy in women

Q. Does the woman have symptoms consistent with FAI (eg, low libido and decreased energy and wellbeing)?

A. *If yes, initiate evaluation.*

Q. Is there an alternative explanation or cause for these symptoms (eg, major depression, chronic fatigue syndrome)?

A. *If yes, manage as appropriate. If no, evaluate further.*

Q. Is the woman in an optimum estrogen state?

A. *If yes, continue evaluation. If no, initiate estrogen replacement.*

Q. Does the woman have laboratory values consistent with a diagnosis of androgen insufficiency?

A. *If yes, continue evaluation. This should include assessment of at least two of three measures of total T, free T, or SHBG. Androgen values should be in the lowest quartile of normal ranges for reproductive age women. If no, consider alternative treatments or referral.*

Q. Does the woman have a specific treatable cause for androgen insufficiency (eg, oral estrogens, oral contraceptive use)?

A. *If yes, treat the specific cause (eg, change medications). If no, consider a trial of androgen replacement therapy.*

Their recommendation, however, was that if total free testosterone concentration is measured, that it be measured by equilibrium analysis, which is the gold standard for the assessment of testosterone levels in the low range. In addition to free or total T concentration measurement, the panel also suggested assessment of SHBG level, because this level determines the concentration of bioavailable androgens.

The assessment of androgen production and bioavailability can be done in several ways. These include measurement of free T and SHBG, total T and SHBG, or free and total T. Based on circadian and menstruation effects on androgen production, the panel suggested that clinicians consider measuring T

values at two points, one measurement in the morning and one measurement during the middle of an ovulatory menstruation cycle. In the postmenopausal women, because adequate estrogen is necessary for the preservation of urogenital health, estrogen status should also be assessed.

Braunstein and colleagues [8] proposed an algorithm for the diagnosis of FAI. After proper estrogen supplementation in the estrogen-deprived woman and exclusion of other possible etiologic causes for the sexual dysfunction and other symptoms, the woman should be considered to have FAI. Further evaluation at this point may include laboratory measurement of free testosterone and DHEA-S. For the laboratory assessment of testosterone, equilibrium dialysis is the recognized method; this includes measurement of total T by immunoassay and a dialyzable fraction of T. Another method, though quicker but less reliable than equilibrium dialysis, includes the direct immunoassay measurement of free testosterone using analog ligand. Free testosterone index, sometimes referred to as free androgen index, is an alternative method for the assessment of free T. This index is a ratio of $100 \times \text{total T level}/\text{immunoactive SHBG concentration}$.

Rivera-Woll [1] suggested some other laboratory tests for the diagnosis of FAI besides free and total testosterone and SHBG levels. The immunoassay of DHEA-S is also an easy and reliable method for androgen level assessment. DHEA-S assays are not affected by diurnal variation and also are not bound to SBHG, making them a useful measure for adrenal androgen production assessment, which is especially useful in menopausal women. Other laboratory values to consider include TSH, estradiol, and FSH levels.

Treatments that have been used for female androgen insufficiency

The most controversial aspect of FAI is its treatment. There are many available options for treatment, including medications, counseling, treating underlying causes, sex therapy, vasoactive substances, and estrogen therapy. Some cases of FAI have shown improvement by psychiatric counseling and assurance. Changing sex techniques and solving relationship issues also can be helpful. Despite the use of various therapeutic interventions, there is no standard treatment available for FAI, especially in androgen use.

Hormonal interventions that have been used for the treatment of FAI include combined estrogen and androgen, oral methyl testosterone, testosterone implants and injections, and oral dehydroepiandrosterone (DHEA). The most work with DHEA-S has been done in women who have adrenal insufficiency. Arlt and colleagues [9] studied the effects of dehydroepiandrosterone therapy in women with adrenal insufficiency. They observed significant improvement in physical and psychologic aspects of female sexual health after 4 months' administration of 50 mg DHEA. DHEA is not FDA approved, because its long-term safety and efficacy profile is not well established. Side effects of DHEA treatment are acne, hirsutism, deepening of voice, alopecia, hepatic injury, weight gain, and sleep apnea.

When considering androgen therapy in the reproductive aged woman, virilization of a female fetus is a potential threat, and counseling regarding this should be done. All women receiving androgen therapy should be counseled about potential androgen effects.

Among the available forms of androgens, oral preparations are used most frequently. Injectable preparations of testosterone have disadvantages of extreme peaks and troughs and injection site discomfort. Testosterone creams, sprays, and gels, available for use in men, have been used in women also [10]. Pellet implants are often used in Europe but are infrequently prescribed in the United States. An option used in the United States is combination esterified estrogen/methyl testosterone oral preparations. These are often used in surgically menopausal women and in naturally menopausal ones. Despite the vast research done in the area of the testosterone patch for women, it is not FDA approved in the United States. Many further clinical trials are underway investigating testosterone therapy for women as a treatment for FAI, but it may take years before an FDA approval is obtained.

In 2005, The North American Menopause Society (NAMS) created a position statement regarding the role of testosterone therapy in postmenopausal women [11]. Some of the recommendations supported by NAMS for testosterone therapy are as follows:

- Testosterone therapy should be considered only for postmenopausal women who have symptoms of decreased sexual desire without any identifiable causes.
- Laboratory testosterone levels should not be considered as diagnostic tests for testosterone insufficiency. They should be evaluated for monitoring supraphysiologic testosterone levels before and after initiation of testosterone therapy.
- Serum lipids and liver function tests should be evaluated before starting testosterone therapy in postmenopausal women, and retesting at 3 months should be considered. If the testosterone levels are stable, annual assessment is advised.
- Testosterone therapy is recommended only with concomitant estrogen therapy.
- Testosterone products available in the United States are specifically formulated for men and have very high concentrations of testosterone. Physicians should reduce doses and monitor blood testosterone levels closely for side effects. Transdermal patches and creams may be preferred over pellet and intramuscular formulations to avoid excessive dosing and discomfort.
- Data on efficacy and safety of testosterone therapy do not support testosterone use in women beyond 6 months.
- Testosterone therapy should not be given to women who have breast or uterine cancer or who have cardiovascular or liver disease.

Regarding nonpharmacologic intervention, currently the only FDA approved mechanical device for the treatment of diminished female arousal is a clitoral therapy device that increases blood flow to the clitoris and labia. The mechanism of increased blood flow is hypothesized to improve genital sensation and sexual satisfaction.

Challenges in female androgen insufficiency diagnosis and treatment

The diagnosis and treatment of FAI poses complex diagnostic and management issues for the clinician caring for women [12,13,14]. The most important drawback for the diagnosis of FAI is not only difficulty in measuring accurate testosterone levels at low levels but also a lack of sensitive, standardized, and validated tests for the clinician to easily assess female sexual function in a busy office setting.

Also, some clinicians measure androgen levels and others do not. Current assays for measurement of testosterone levels were developed for high circulating levels in men; therefore, they lack sensitivity in measuring low levels that are found in women. Precise estimation of testosterone concentration is further complicated by lack of normal reference ranges for testosterone levels in women. There are no data available on normal testosterone levels after adjusting for age, menopausal status, and other factors. Another problem for the diagnosis is peripheral biosynthesis of androgens from adrenal androgen precursors, which makes the measurement of androgens more difficult, because these have androgen actions without causing an increase in total androgen levels.

For treatment, several clinical trials have shown improvement in women who have androgen deficiency after androgen therapy [15,16,17]. The understanding of benefits and risks of androgen replacement therapy is evolving. The complexity of female sexuality and factors associated with sexual satisfaction make it difficult to treat androgen insufficiency, because many causes may contribute to symptoms. Counseling and education of women about sexual myths and misconceptions should be a part of the management intervention for all women who have female sexual dysfunction, including women who have FAI.

Because most women who have FAI are diagnosed after menopause, and because most women live one third of their lives after menopause, androgen therapy for symptomatic menopausal women, especially surgically menopausal women, is a high priority for further clinical trials. Clinical emphasis should be placed on the establishment of effective and standardized diagnosis and treatment protocols for FAI.

Summary

FAI, seen commonly and often caused by aging and ovarian dysfunction, still presents a challenge to clinicians because of some unresolved and

unattended aspects of the condition, including standardized diagnosis and management. Although the use of androgens in women who have FAI has been shown to be effective, there are no FDA approved androgen preparations available at this time for women. Large scale, long-term, controlled trials focusing on establishment of valid and standardized diagnosis and treatment options are needed.

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