

Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment

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Objective: To evaluate the evidence for and against androgen insufficiency as a cause of sexual and other health-related problems in women and to make recommendations regarding definition, diagnosis, and assessment of androgen deficiency states in women.

Design: Evaluation of peer-review literature and consensus conference of international experts.

Setting: Multinational conference in the United States.

Patient(s): Premenopausal and postmenopausal women with androgen deficiency.

Intervention(s): Evaluation of peer-review literature and development of consensus panel guidelines.

Result(s): The term "female androgen insufficiency" was defined as consisting of a pattern of clinical symptoms in the presence of decreased bioavailable T and normal estrogen status. Currently available assays were found to be lacking in sensitivity and reliability at the lower ranges, and the need for an equilibrium dialysis measure was strongly emphasized. Causes of androgen insufficiency in women were classified as ovarian, adrenal, hypothalamic-pituitary, drug-related, and idiopathic. A simplified management algorithm and clinical guidelines were proposed to assist clinicians in diagnosis and assessment. Androgen replacement is currently available in several forms, although none has been approved for treatment of sexual dysfunction or other common symptoms of female androgen insufficiency. Potential risks associated with treatment were identified, and the need for informed consent and careful monitoring was noted. Finally, the panel identified key goals and priorities for future research.

Conclusion(s): A new definition of androgen insufficiency in women has been proposed along with consensus-based guidelines for clinical assessment and diagnosis. A simplified management algorithm for women with low androgen in the presence of clinical symptoms and normal estrogen status has also been proposed. (Fertil Steril® 2002;77:660-5. ©2002 by American Society for Reproductive Medicine.)

Key Words: Androgen deficiency states, bioavailable testosterone, sex hormone-binding globulin, low libido, androgen replacement therapy, female sexual dysfunction

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1. OVERVIEW

Despite the ubiquitous role of circulating androgens as prohormones for other steroids (e.g., estrogen), in addition to their direct effects on diverse physiological and behavioral systems, the role of androgens in women has

been relatively neglected. Historically, androgens have been identified with masculinity or male sexual function, which has undoubtedly contributed to a lack of recognition of androgen effects in women. In fact, androgens are necessary not only for the development of reproductive function and hormonal homeostasis

in women but also represent the immediate precursors for the biosynthesis of estrogens. Androgens affect sexual desire, bone density, muscle mass and strength, adipose tissue distribution, mood, energy, and psychological well-being. Consequently, imbalance in androgen biosynthesis or metabolism in women may have undesirable effects on any or all of these domains. The role of androgens in female health and well-being is a topic of growing interest and concern, although controversy exists concerning the existence of androgen deficiency states and their clinical diagnosis or management.

An international consensus conference on androgen deficiency in women was convened in Princeton, New Jersey, on June 28 and 29, 2001, under the auspices of the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School. The conference included participants representing the fields of epidemiology, endocrinology, pharmacology, obstetrics and gynecology, urology, psychology, psychiatry, and women's health. The conference reviewed findings in several areas: [1] androgen production and mechanisms of action; [2] androgen and normal development; [3] androgen deficiency states and their clinical sequelae; [4] clinical assessment and diagnosis; and [5] research issues and priorities. The complete proceedings of this conference are presented in the accompanying supplement.

On the basis of the evidence presented, the following consensus statement was developed concerning the role of androgens in women's health and well-being. The term "female androgen insufficiency" was proposed as a new descriptive or diagnostic term to be applied in specific circumstances described below. Guidelines for assessment and diagnosis of androgen insufficiency in women were considered in detail, and a new diagnostic guide or algorithm was developed. Specific recommendations for laboratory testing were proposed. While the potential value of androgen replacement in particular circumstances was noted, the risks and benefits of individual therapies were not addressed. Clinical trial data are insufficient, at present, to recommend any one form of androgen replacement over another. In view of the potential significance and lack of recognition of the role of androgens in women's health, specific research goals and priorities were identified.

2. ANDROGEN PRODUCTION AND BIOSYNTHESIS IN WOMEN

The term "androgen" is generally applied to the class of C19 steroids, which are produced by the gonads and the adrenals in both sexes (1, 2) and include T, DHEA, DHEAS, androstenedione (A), and 5 α -dihydrotestosterone (DHT). Of the androgenic steroids, T and DHT have the most potent biological activity. In women, approximately 25% of androgen biosynthesis takes place in the ovaries, 25% is produced

by the adrenal gland, and the remainder is produced at tissue sites in the periphery (3, 4). In the ovaries, cholesterol is metabolized to pregnenolone, which serves as the major precursor for the synthesis of sex steroids. Biosynthesis of T from pregnenolone proceeds via participation of several key enzymes in two interrelated pathways (i.e., $\delta 5$ or $\delta 4$ pathways). Circulating T functions as a prohormone, with conversion in target tissues to DHT or E₂. DHEAS, DHEA, and A are the major sources of peripheral androgen production in women. Whereas DHEAS is derived almost entirely from the adrenals and is converted to DHEA by steroid sulphatase, DHEA is produced by both the adrenals and ovaries. A is similarly derived from both ovarian and adrenal sources. Androgen secretion by the ovaries and adrenals is stimulated by LH and ACTH, respectively, in addition to other intraglandular mechanisms. The mechanisms by which DHEA and DHEAS are converted to active sex steroids are described in detail by papers in the accompanying supplement by Burger (5) and Simpson (6). As noted by both authors, circulating androgens are found in much higher concentrations than estrogens in both genders and are involved in a variety of biochemical and physiological functions.

Androgens act on multiple tissue and receptor sites. These include central nervous system pathways in the hypothalamus and limbic system and important peripheral sites such as bone, breast, pilosebaceous unit, skeletal muscle, adipose, and genital tissues. T, DHT, and DHEA have direct actions on bone, although T and DHEA also act on these sites via conversion to E₂ and estrone. The effects of androgens may be mediated by conversion to estrogens. For example, T action in the brain may require conversion to estrogen via the aromatase enzyme. Alternatively, T may act directly in the brain via central androgen receptors.

Androgen insufficiency in women occurs for several reasons. Recognized causes include hypopituitarism, Addison's disease, corticosteroid therapy, ovarian failure or oophorectomy, and oral estrogen replacement therapy or oral contraceptive use. Since T binds substantially to sex hormone-binding globulin (SHBG), hormonal therapies that are associated with increased SHBG levels in women may result in a corresponding decline in free or bioavailable T. These and other mechanisms are addressed in detail in the accompanying papers by Shifren (7), Davis (8), Sarrel (9), and Simon (10). In contrast to men, physiological mechanisms regulating the homeostatic control of androgens in women have not been clearly delineated. This is an important area for future research.

3. ANDROGEN ASSAYS AND MEASUREMENT IN WOMEN

The need for accurate and reliable measurement of androgens was a major focus of the consensus panel. Current, commercially available assays were noted to be deficient in

several respects, particularly in regard to sensitivity and reliability at the lower ranges of measurement. Three specific recommendations were made. Despite multiple sources of production and biosynthesis, total androgen production is best reflected by the total T concentration. A second issue concerns the clinically relevant T fraction to be used. The panel recommended specifically that free T concentration, as measured by equilibrium dialysis, be adopted as the "gold standard" for laboratory assessment of bioavailable T in women. Lastly, when either total or free T is measured, the concentration of circulating SHBG should be taken into account. Independent of the source of production of T, SHBG levels can be influenced by a number of factors and will determine the amount of T that is bioavailable, i.e., a lowered bioavailable T level may result from impaired T production or from increased SHBG levels in the presence of normal T production. For this reason, it is always necessary to consider SHBG levels in the assessment of bioavailable T in women.

Clinical assessment of both androgen production and androgen availability can be achieved by measurement of two of three essential values. These include either total T and SHBG, free T and SHBG, or free T and total T. Ideally, T values should be obtained in the morning hours and in the middle third of the menstrual cycle in normally cycling premenopausal women. These latter recommendations are based on current concepts of circadian and menstrual cycle effects on androgen production in women, although the actual range of variability associated with these factors has not been well documented. The Free Testosterone Index (total T/SHBG) correlates well with free or bioavailable T and can be used as a substitute. Free T assays, whether assessed directly or by analogue methods, are not well validated for women. Further development and validation of specific T assays for women were identified as major goals for future research.

DHEAS is the most useful measure of adrenal androgen production in women. Current assays for DHEAS are robust, reliable, and not affected by diurnal variation. DHEAS should be measured if there are specific concerns regarding an adrenal cause of androgen insufficiency. DHEAS deficiency has been related to female sexual dysfunction in some studies. This issue is addressed in detail in the accompanying paper by Spark (11).

The potential role of salivary assays was considered. Although these may have limited value in research settings, salivary T assays were not considered sufficiently accurate or reliable at present for clinical use. Potential biologic markers for androgen insufficiency in women, such as muscle strength, bone density, or pilosebaceous unit integrity, were also reviewed. Despite their potential importance as clinical or research endpoints, these biological markers were not considered to be sufficiently sensitive or specific for diagnostic purposes.

In summary, the development of a sensitive and reliable laboratory assay of bioavailable T is a major clinical and research priority. Free T concentration, as measured by equilibrium dialysis, was recommended as the optimal assay in this regard. Total T concentration should be evaluated as an index of overall androgen production, and SHBG levels should be assessed when direct measures of free or bioavailable T are not available. The Free Testosterone Index correlates well with free or bioavailable T and can be used as a substitute measure for clinical purposes. DHEAS assays are readily available and are useful in assessing adrenal androgen production. Salivary measures are not recommended at the present time.

4. FEMALE ANDROGEN INSUFFICIENCY: EVIDENCE FOR A CLINICAL SYNDROME?

Epidemiological and clinical trial data were reviewed concerning the potential effects of androgen insufficiency in women on various aspects of female health and well-being. While there is increasing evidence for symptomatic effects of androgen deficiency under specific conditions or in particular etiological subgroups, this evidence may be confounded in some instances by the effects of pharmacological or supraphysiological androgen replacement regimens. Recent trials have provided more adequate controls for these effects. The best-documented causes of female androgen insufficiency are hypopituitarism, adrenal insufficiency, ovarian failure, and oophorectomy.

Androgen insufficiency in women is not a specific consequence of natural menopause but may occur secondary to the age-related decline in both adrenal and ovarian androgen production. In women with ovarian, adrenal, or central dysfunction, androgen insufficiency may occur at a younger age. As current assays have limited sensitivity in the lower ranges found normally in women, serum testing alone is not reliable for making the diagnosis of androgen insufficiency in the absence of clinical symptoms and a clear physiological reason for decreased androgen production. Androgen replacement in reproductive age women should be carefully considered because of the additional risk of virilization of a female fetus. Additionally, the benefits of androgen replacement in premenopausal women have not been conclusively demonstrated at the present time.

Considering the lack of sufficient epidemiological data and limitations of current laboratory assays, a conservative definition of androgen insufficiency in women was proposed based on three essential criteria: First, clinical symptoms of androgen insufficiency should be clearly present. Symptoms of androgen insufficiency most often reported in the literature include [1] a diminished sense of well-being or dysphoric mood; [2] persistent, unexplained fatigue; and [3] sexual function changes, including decreased libido, sexual recep-

tivity, and pleasure. Vasomotor instability or decreased lubrication have been observed in some studies, even in women who are adequately estrogenized. Other potential signs or symptoms include bone loss, decreased muscle strength, and changes in cognition or memory. As the most common presenting symptoms are nonspecific, symptoms alone are not sufficient for the diagnosis of androgen insufficiency. Individual presenting complaints (e.g., diminished energy, low libido) can be symptomatic of other common disorders, such as depression.

Second, since estrogen effects are also strongly linked to mood, psychological well-being, and sexual function in women, a diagnosis of androgen insufficiency should only be made in women who are adequately estrogenized. This could include normally cycling premenopausal women or postmenopausal women receiving estrogen replacement therapy. The importance of assessing androgenic function in the context of the estrogenic milieu is reviewed in the accompanying papers by Sarrel (9) and Simon (10).

Third, in the absence of a sufficiently sensitive assay or absolute threshold for androgen insufficiency in women, free T values should be at or below the lowest quartile of the normal range for the reproductive age (20–40 years), in conjunction with the presence of clinical symptoms and adequate estrogen status. Low androgen values defined in this way provide a clinically useful, albeit arbitrary, criterion for establishing a diagnosis of androgen insufficiency. Low androgen levels do not constitute a sufficient basis for establishing the diagnosis in the absence of other clinical signs or symptoms. Selection of the lowest quartile criterion was based, in part, on the insensitivity of current assays at the lower ranges, in addition to the potential risks of androgen replacement in women with normal or elevated androgen levels before treatment.

Further research is urgently needed to determine the range of normal values of the various androgens in women, particularly for the different phases of the reproductive life cycle. The potential association with other demographic variables, such as age and ethnicity, as well as other health conditions, also needs to be assessed. Increased diagnostic precision will only be achieved with the availability of more sensitive assays and comparative data in normal and clinical populations.

5. DIFFERENTIAL DIAGNOSIS OF ANDROGEN INSUFFICIENCY IN WOMEN

The pattern of symptoms consistent with female androgen insufficiency may be indicative of or causally related to other medical, psychiatric, or psychosocial factors. If the pattern of symptoms observed appears to be due primarily to one or more of the following conditions, these should be addressed before considering a trial of androgen replacement: [1]

major life stress or relationship conflicts; [2] thyroid disease (i.e., hypo- or hyperthyroidism); [3] major metabolic/nutritional disorders (e.g., iron or vitamin D deficiency) or other causes of chronic fatigue (e.g., Lyme disease, chronic fatigue syndrome); and [4] psychiatric disorders (e.g., major depressive disorder). Androgen insufficiency may coexist with any or all of the above conditions.

In evaluating androgen insufficiency in women, specific etiological factors or determinants should also be considered. Where possible, therapy should be aimed at reversing or ameliorating the specific cause of deficiency. In other instances, androgen replacement should be considered if medically indicated. Five major categories or types of etiology were identified, as follows:

1. Ovarian (chemotherapy, radiation therapy, oophorectomy)
2. Adrenal (adrenal insufficiency, adrenalectomy)
3. Hypothalamic-pituitary (hypopituitarism)
4. Drug-related (corticosteroids, antiandrogenic agents, oral contraceptives, oral estrogen replacement therapies)
5. Idiopathic

Other potential etiological conditions or predisposing factors have been implicated in some studies. These include anorexia nervosa and various immunologic disorders, such as rheumatoid arthritis, systemic lupus erythematosus, and HIV-AIDS. The major cause of androgen deficiency in these latter instances is possibly adrenal, although the specific pathophysiology is uncertain. Moreover, a specific role for androgen replacement in the treatment of these conditions has not been established. Finally, it has been suggested that androgen therapy may be of benefit in premenstrual syndrome and other menstrual disorders in women. This hypothesis is lacking in empirical support, and clinical trials in this area have been inconclusive.

6. MANAGEMENT GUIDELINES

Before initiating a trial of androgen replacement therapy, a comprehensive clinical assessment should be performed in all cases. This evaluation should include a detailed medical and psychosocial history, physical examination, and laboratory testing. A major goal of this conference was to develop evidence-based guidelines for determining which patients should be considered for treatment of suspected androgen insufficiency. As noted above, the panel emphasized that clinical manifestations of androgen insufficiency are highly variable, often nonspecific, and may be associated with multiple potential causes or etiological factors. To assist clinicians in making a diagnosis and initiating therapy, a simple management algorithm was proposed (Table 1).

7. TREATMENT SELECTION

Many factors should be taken into consideration in selecting the specific mode of treatment for individual cases.

TABLE 1**Decision-making algorithm for initiating androgen therapy in women.**

- Q. Does the woman have symptoms consistent with female androgen insufficiency (e.g., low libido, decreased energy and well-being)?
 A. *If yes, initiate evaluation.*
- Q. Is there an alternative explanation or cause for these symptoms (e.g., 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 (e.g., oral estrogens, oral contraceptive use)?
 A. *If yes, treat the specific cause (e.g., change medications). If no, consider a trial of androgen replacement therapy.*

Bachmann. Female androgen insufficiency. Fertil Steril 2002.

These should include consideration of safety and efficacy data related to the particular form of treatment, potential contraindications or adverse reactions, cost and lifestyle factors, and patient preferences. While the advantages or limitations of specific forms of androgen replacement were not the major focus of this conference, several general observations regarding androgen replacement in women were noted.

Approved androgen replacement therapies are not available in most countries for treatment of female sexual dysfunction. Clinical trials are currently under way in several countries to evaluate the safety and efficacy of various therapies in women with androgen insufficiency and symptoms of sexual dysfunction. Ideally, treatment recommendations should be based on the results of large, randomized, placebo-controlled clinical trials.

Physicians currently prescribing androgen replacement therapy on an "off-label" basis, including T supplements or DHEA, should ensure that patients receive regular assessments for safety and efficacy. Patients should also be fully informed that these therapies are not currently approved for this indication and that safety and efficacy remain unproved.

8. POTENTIAL RISKS OF ANDROGEN REPLACEMENT

Given the paucity of long-term, controlled trials, patients should be fully informed of potential risks and carefully monitored for potential adverse reactions. Potential side effects of androgen therapy include acne, weight gain, excess facial and body hair, permanent lowering of the voice, emotional changes (e.g., increased anger), and adverse lipid changes. Based on available clinical trial data, these side effects are infrequent if androgen levels are maintained within normal physiological ranges. Lowered HDL cholesterol, increased hematocrit levels, and abnormal liver function tests have been reported with certain oral T preparations.

Potential virilization of a female fetus is a serious risk in reproductive age women. As androgens are converted to estrogens in vivo, estrogenic side effects are also potential consequences of androgen therapy, including increased risk of breast and ovarian cancer.

9. RESEARCH NEEDS AND PRIORITIES

A major focus of the consensus panel was to identify critical research needs and priorities. Six specific areas of research priority were identified as follows:

1. To characterize normal androgen levels in women by [a] decade of life, [b] life cycle stages (i.e., childhood, puberty, reproduction, postreproduction), and [c] race and ethnic background.
2. To develop sensitive and reliable assays for total and free T measurement in the lower ranges of normal for women. Once sufficiently sensitive assays have been developed, to evaluate the relationship between laboratory values and specific symptoms or clinical sequelae of androgen insufficiency in women.
3. To identify stable biologic markers of androgen insufficiency in women. The effects on bone density, muscle strength, and cognitive function, in particular, warrant further investigation.
4. To determine the mechanism of sexual dysfunction associated with androgen insufficiency in women. In particular, the role of central mechanisms versus peripheral physiological actions of androgens in female genital tissues warrants further investigation. Studies are also needed to assess the effects of diminished free T secondary to increased SHBG levels with oral contraceptive use or oral estrogen therapies and the associated effects on sexuality and mood.
5. To evaluate the safety and efficacy of specific androgen replacement therapies by means of large, randomized, placebo-controlled trials of sufficient duration (e.g., 6–12 months). These trials should be conducted with well-characterized regimens that achieve physiological, as opposed to supraphysiological, concentrations of T in women with an-

drogen insufficiency diagnosed according to the above guidelines. Comparator and long-term trials are also urgently needed.

6. Finally, studies are needed to identify physiological or clinical markers that might predict responsiveness to therapy in specific patient groups. Clinical outcomes for future research might include measures of bone density, muscle mass/strength, cognitive function, and mammographic density or other potential markers of breast cancer risk. Variability among women in the central effects of androgens and the differential effects of low androgen levels on mood and sexual behavior, in particular, are of special interest. This latter issue is addressed in detail in the accompanying paper by Bancroft (12).

10. CONCLUSION

An international consensus conference was convened to consider the role of androgens in women's health and well-being. Based on a review of the available evidence and clinical practice in the area, conclusions and recommendations were made as follows: [1] The role of androgens in women's health has been generally neglected and is not well recognized or understood. The signs and symptoms of androgen insufficiency are based on clinical observation and intervention trials but have yet to be confirmed by large-scale epidemiological studies. [2] Current androgen assays are unsatisfactory primarily because of their lack of sensitivity or reliability at the lower ranges of normal. Development of an equilibrium dialysis assay is highly recommended for optimal assessment of bioavailable androgen in women. [3] In the absence of an optimal assay, the free testosterone index should be calculated for diagnostic purposes using a total T assay with appropriate sensitivity to measure the normal female range reliably. Since androgen insufficiency may result from increased SHBG levels in the presence of normal T production, it is necessary to consider SHBG levels in the clinical assessment of bioavailable T in women. [4] Female androgen insufficiency may occur under

certain conditions and should be carefully evaluated by a combination of clinical symptoms and laboratory testing. [5] A diagnostic algorithm has been proposed, which includes evaluation and normalization of estrogen status. [6] Androgen replacement should only be considered when all diagnostic criteria are met and alternative diagnoses have been excluded. [7] Patients receiving androgen replacement therapy should be fully informed of potential risks and carefully monitored for potential adverse effects of treatment. [8] Key research priorities and needs have been identified.

Overall, a strong consensus was reached regarding the need for greater understanding of the role of androgens in women's health. The need for large-scale, clinical trials and better epidemiological research was emphasized. The present guidelines were developed to provide a well-balanced and evidence-based approach to the clinical management of androgen insufficiency in women and to identify critical issues and problems for further research.

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