FERTILITY AND STERILITY®
VOL. 77, NO. 4, SUPPL 4, APRIL 2002

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

When to suspect androgen deficiency other than at menopause

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Objective: To review causes of female androgen insufficiency (FAI) other than menopause.

Design: A review of the available literature in this field.

Result(s): Androgen levels decline with increasing age during the reproductive years in healthy women and vary little or not at all across menopause, with controversy as to whether levels change in the postmenopausal years. Thus the premenopausal decline in androgens potentially is the most common cause of female androgen insufficiency (FAI), whereas natural menopause in itself is not a cause of androgen deficiency. Pathophysiological causes of FAI can be divided into those that affect ovarian androgen production, those that affect adrenal androgen production, and combined deficiency states. Surgical menopause is characterized by an abrupt onset of symptoms, in contrast to a more insidious onset of relatively nonspecific symptoms in women who have FAI due to aging.

Conclusion(s): The decline in testosterone with normal aging before menopause may well be the most common cause of FAI, although many women do not present with symptoms and most are not diagnosed until they have reached menopause. (Fertil Steril® 2002;77(Suppl 4):S68–71. ©2002 by American Society for Reproductive Medicine.)

Key Words: Female androgen insufficiency, depression, menopause

Female androgen insufficiency (FAI) is increasingly accepted as a valid clinical entity. Affected women complain of persistent fatigue, lack of well-being, and loss of libido, symptoms easily attributable to psychosocial and environmental factors. However, when these symptoms are clearly linked to low circulating bioavailable testosterone (T) levels, androgen replacement may result in significant improvement in symptomatology. Possible causes of FAI are listed in Table 1. The greatest acceptance for the concept of FAI is for women who have undergone surgical menopause and who have persistent symptoms despite apparently adequate estrogen therapy. That naturally postmenopausal women experience symptoms due to androgen insufficiency is more controversial. This is primarily because of the evidence that androgen levels do not acutely change with menopause, as described later in this article. Women who have symptoms of FAI during their perimenopausal or postmenopausal years are likely to have had symptoms before this time or to have exacerbation of their symptoms with the development of estrogen deficiency or with treatment with oral estrogen therapy.

CAUSES OF ANDROGEN INSUFFICIENCY OTHER THAN NATURAL MENOPAUSE

The mean circulating levels of T decline continuously with increasing age from the early reproductive years, such that the levels of women in their 40s are approximately half of those of women in their 20s (1). Although the percentage of free T does not vary with age, an absolute decline in free T with age has been reported. DHEAS levels also fall linearly with age, and this contributes to the decline in the level of their metabolite, T (2, 3). In the late reproductive years, there is failure of the midcycle rise in free T that characterizes the menstrual cycle in young ovulating women (4). This occurs despite preservation of normal free T levels at other phases of the cycle.

Whether the ovaries are a significant source of androgen production in postmenopausal women is controversial. Earlier studies have

Received October 16, 2001; revised and accepted January 9, 2002.
Reprints will not be available.

0015-0282/02/$22.00
PII S0015-0282(02)02977-1

TABLE 1

Causes of androgen deficiency in women.

Normal aging
Symptomatic premenopausal or postmenopausal women with low bioavailable T
Ovarian insufficiency
Unilateral or bilateral oophorectomy
Hysterectomy
Premature menopause after chemotherapy or radiotherapy
Adrenal insufficiency
Adrenal failure or surgery
Combined
Hypopituitism
Autoimmune adrenal and ovarian failure
Iatrogenic
Treatment with exogenous oral estrogen
Antiandrogen therapy
Chronic glucocorticosteroid treatment

Davis. Androgen deficiency other than at menopause. Fertil Steril 2002.

TABLE 2

Proposed clinical cluster of androgen deficiency symptoms.

Loss of libido
Lack of desire to be intimate
Loss of motivation
Flat mood
Diminished well being
Blunted motivation[a]

[a] Dominant feature.

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indicated that the postmenopausal ovary functions as a gonadotropin-driven, androgen-producing gland (5), resulting in free T levels in older women being equivalent to those in premenopausal women when adjusted for body mass index (6). However, it now appears that after the decline in total and free T with age in the premenopausal years (1), levels remain stable across the menopausal transition (7–9) and then either remain stable or continue to decline with the gradual decline in adrenal function with increasing age (10). In a recent series of experiments assessing the steroidogenic potential of the postmenopausal ovary, Couzinet and others (11) demonstrated that this tissue is not a significant source of postmenopausal androgens. This contrasts with findings of earlier studies that suggested that after natural menopause, ovarian stromal hypertrophy and hyperplasia may persist or develop, possibly secondary to elevated LH levels and individual sensitivity, resulting in increased T production (12). After menopause, peripheral conversion of androstenedione (A) remains a major source of circulating T (13).

A sudden decline in androgens is a feature of ovariectomy, with both T and A decreasing acutely by about 50% (14). Unilateral ovariectomy or hysterectomy alone are also associated with lower circulating total and bioavailable T (6). Other iatrogenic causes of T deficiency include chemical ovariectomy, for example, the use of GnRH antagonists for the treatment of fibroids or endometriosis after chemotherapy or radiotherapy.

The administration of exogenous estrogens or glucocorticosteroids suppresses ovarian and adrenal androgen production, respectively. Use of either the combined oral contraceptive pill or oral estrogen replacement therapy results in lower circulating androgens (15, 16). This is a result of an increase in SHGB combined with suppression of LH production by the pituitary and hence lessened stimulus for ovarian stromal production of T. These effects are amplified in older women whose overall androgen production is declining (15, 16). Treatment with oral glucocorticosteroids results in ACTH suppression and hence in reduced adrenal androgen production (17).

In the premenopausal years, other pathophysiological states, such as hypothalamic amenorrhea and hyperprolactinemia, are characterized by low circulating T levels and bone loss. Women who have experienced premature ovarian failure have lower circulating levels of DHEAS, A, and T (18) and similarly experience significant loss of bone that not uncommonly persists, despite adequate standard estrogen–progestin therapy (19). Hence it is likely that young women with either ongoing hypothalamic amenorrhea or premature ovarian failure require T replacement to prevent progressive bone demineralization.

Women who have panhypopitutism have loss of both adrenal and ovarian function, as do women who have combined Addison's disease and premature ovarian failure. Traditionally, such women have hormonal replacement regimens that exclude androgen supplementation, despite their profound androgen deficiency (20).

Other conditions that have been associated with FAI include premenstrual syndrome (21), management of muscle wasting associated with HIV infection, and systemic lupus erythematosis and rheumatoid arthritis (22–24).

CONSEQUENCES OF ANDROGEN INSUFFICIENCY

The cluster of symptoms that appears to characterize FAI includes diminished well-being, flattened mood, loss of motivation, fatigue, and loss of libido (Table 2) (25). The diagnosis should not be made in the setting of concurrent estrogen deficiency, and treatment with androgen should be deferred until the individual has been on adequate estrogen therapy for several weeks. This is because estrogen therapy alone may alleviate the presenting symptoms and obviate the need for additional androgen replacement in some women. However, some of the consequences of FAI may not be

immediately apparent, such as bone loss, muscular decline, and loss of sexual hair, and the need for androgen therapy should remain under constant review.

Women may experience symptoms of androgen deficiency because of aging in their late reproductive years, as early as in the late 30s. The symptoms caused by this decline with age usually develop insidiously, and most women are not aware that such symptoms have a biological basis. That many women do not report symptoms until the menopause does not mean that the symptoms have not been present earlier. Indeed, it is well known that women who report loss of libido after menopause have commonly had a similar problem in the premenopausal years. Young women with primary ovarian failure may not be able to identify their own symptoms. That is, it is difficult for some women to identify loss of libido if they have never experienced sexual interest. Hence, physicians need to be aware of the possibility that androgen insufficiency is causing nonspecific symptoms in such women, who thus may be responsive to androgen therapy.

Symptoms are more pronounced in women who have undergone a surgical menopause because of the abrupt cessation of T production by the ovaries. Symptoms may also occur in premenopausal women with either spontaneous or iatrogenic androgen deficiency and in naturally menopausal women.

Androgens appear to significantly influence behavior and mood (26, 27), and we have proposed that FAI may contribute to the greater rate of depression in women compared with men. Studies in postmenopausal women have shown improved mood and well-being with androgen replacement (26, 28), although little is known of the effect of T therapy for premenopausal women. We conducted a randomized, placebo-controlled cross-over study of the effects of transdermal T on mood and sexual function in premenopausal women and observed significant improvement in sexual function and restoration mood and well-being scores to the normal range with active therapy (Goldstat R, Briganti E, Tran J, et al., abstract).

Further studies are warranted to not only reaffirm the changes in androgens with age in women but also to document more fully the relationships between endogenous bioavailable T, DHEA, and DHEAS and mood and sexual interest in women.

DIAGNOSING FAI

Biochemical measurements that should be performed to diagnose FAI in nonmenopausal women include total T, sex hormone–binding globulin (SHBG), free androgen index, as well as any other clinically indicated investigations such as thyroid function and iron studies. Free T alone is not a particularly useful measurement because it does not indicate total T production or how much is unavailable because of high binding to SHBG.

If a woman is taking exogenous oral estrogen and has a normal T level but high SHBG (therefore low bioavailable T), then she should be initially changed to nonoral therapy (in the case of hormone replacement therapy), and the profile should be repeated and the clinical assessment reconducted after 6 to 8 weeks. This may obviate the need for T therapy. Similarly, discontinuing oral contraceptive pill use in young women may be effective.

In general, total T is measured with assays that do not discriminate low T from mid to low normal range. As most laboratories do not use highly sensitive total T assays, a woman with a markedly decreased T level may have a level reported within the normal range; we verified this observation recently by comparing values between a standard and a highly sensitive assay. Hence, until more sensitive assays become routine, women manifesting characteristic symptoms who have a total T below the lower quartile of the normal range and an SHBG level that is normal or elevated should be offered treatment based on clinical assessment.

CONCLUSIONS

Most hormones have a physiological window, or normal range, outside which there is either deficiency or excess. Testosterone deficiency in the past has been underdiagnosed, in part because the symptoms are nonspecific and masquerade as other clinical entities such as depression and in part because of the inability to measure low circulating levels with commonly used techniques. Recognition of the physiological decline in T and other androgens with age and of other causes of FAI will enable greater sensitivity for the diagnosis. There is also a need for availability of specific therapies for women.

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