

The hypoandrogenic woman: pathophysiologic overview

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Objective: To review the pathophysiologic changes associated with androgen insufficiency in the female.

Design: A review of the English-language literature from 1940 to 2001.

Conclusion(s): Data suggest that diminished androgen levels, most frequently noted in the surgically menopausal patient, may be associated with a number of symptoms including reduced sexual libido and desire, loss of motivation, flat affect, and reduced energy. Lack of consensus in defining abnormally low values for free and total serum androgen levels have made the definition of hypoandrogenic states difficult. (Fertil Steril® 2002;77(Suppl 4):S72-6. ©2002 by American Society for Reproductive Medicine.)

Key Words: Androgen insufficiency, surgical menopause, sexual dysfunction, diminished quality of life

Although androgen excess disorders, such as polycystic ovary syndrome and congenital adrenal hyperplasia, are well recognized and widely treated, androgen deficiency in women is also recognized by many researchers and clinicians as an endocrinopathy with equally significant pathophysiologic consequences. Whereas the typical signs of excessive androgen levels include acne, alopecia, menstrual disorders, infertility, insulin resistance, abnormal glucose tolerance, android obesity, dyslipidemia, and frank virilization, the signs and symptoms of androgen deficiency in the female can be equally dramatic (Table 1, Table 2). Also, women with hyperandrogenism typically seek medical intervention to treat the effects of virilizing stigmata on their appearances or because of menstrual irregularity and infertility. These are classic presenting signs and symptoms of this pathophysiologic state, therefore, the diagnosis of the cause of their complaints is, in most patients with hyperandrogenism, clinically obvious. The major question to be answered by the clinical workup is whether the excessive androgenicity is from elevated androgen levels or enhanced receptor sensitivity.

For women presenting with androgen deficiency, in contrast, the symptoms are often not pathognomonic solely for hypoandrogenism, but can have diverse etiologies, including psychiatric or psychosocial causes. Another differ-

ence between hyperandrogenism and hypoandrogenism states is that the medical community universally accepts hyperandrogenism as a distinct clinical entity, whereas many clinicians question the validity of hypoandrogenism as a specific diagnosis. Instead, it is often believed that other etiologies can explain symptoms of low sexual desire and other sexual dysfunctions, a decline in quality of life, including loss of energy and motivation, and other physical symptoms (e.g., reduction in muscle mass). In addition, unlike other hormonal measurements, the sensitivity of testosterone assays has not been consistent in the female. Although, in light of these assay difficulties, controversy also exists regarding the range of normal androgen values for women and, therefore, whether there is an absolute level at which female androgen insufficiency exists.

Because of the inability to accurately measure the serum marker, prostaglandin, it should be noted that another gynecologic disorder, primary dysmenorrhea, was not validated or widely accepted until recently. For example, it had long been recognized that many women had dysmenorrhea with their menstrual flow. Before the link between ovulation, progesterone production by the corpus luteum, and prostaglandin synthesis, many women were told that pain with menses was due to psychological stresses. Recent clinical trials have validated

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TABLE 1**Androgen excess.**

Acne
 Alopecia
 Hirsutism
 Menstrual disorders
 Infertility
 Insulin resistance
 Abnormal glucose tolerance
 Android obesity
 Dyslipidemia
 Frank virilization
 Voice change
 Clitoral changes
 Hypertension

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the role of prostaglandin in causing this type of pelvic pain. It should also be noted that dysmenorrhea can be due to pathologic causes such as endometriosis and pelvic inflammatory disease, and that not all menstrual cramps are solely due to an increase in prostaglandin levels.

ANDROGEN INSUFFICIENCY: HISTORICAL PERSPECTIVE

Some clinicians still question whether androgens can decrease to the point in the female where signs and symptoms of insufficiency are caused. Although this is not generally appreciated, replacement of androgen for women with symptoms of hypoandrogenicity has been recognized in the medical literature as a clinical entity since the 1940s, which was about the same time that estrogen replacement therapy was introduced (1, 2). Many of the early articles on this topic clearly identified signs and symptoms of androgen insufficiency as distinct from estrogen insufficiency and reported successful treatment of the affected women with the addition of androgen replacement (3). In the 1940s, Geist and Salmon reported a prospective case series of 422 postmenopausal women who were treated with testosterone and estrogen for the relief of menopausal symptoms with marked success (1). A decade later, other investigations noted similar findings. For example, Greenblatt and colleagues reported on a prospective, double-blind, placebo controlled study of 31 subjects who were treated with methyltestosterone and diethylstilbestrol (2). These subjects reported improved well being, enhanced libido, decreased hot flushes and amelioration of other menopausal symptoms with both hormones as compared with either hormone alone or placebo (2).

Similarly, even the issue of diminished quality of life at the time of menopause was addressed during this early time period. For example, Birnberg and Kurzok reported reduced irritability, nervousness, and fatigue in their prospective,

case series of 61 postmenopausal women given estradiol and methyltestosterone (4). In 1959, Waxenberg et al. reported an association between diminished sexual desire and decreased testosterone levels in women (5). Other reports followed, showing improvement in menopausal symptoms with the addition of androgen to hormone replacement therapy, the inference being that androgen as well as estrogen was depleted with the menopause. Clinical trials during subsequent decades, however, focused primarily on estrogen replacement.

A possible explanation for this bias is that, until recently, androgen was considered the “male” hormone, and estrogen was the “female” hormone. Therefore, women were reluctant to take androgen replacement for fear of virilization, especially the growth of unwanted facial hair. Scant research was conducted on androgens in women because of this pervading attitude. Today, although there are still myths that circulate in the lay literature, the biological need for both androgens and estrogens in the female is better understood.

ANDROGENS: ROLE IN THE FEMALE

Data are clear that adequate intrinsic androgen production is essential for normal female embryologic development, as well as for normal sexual behavior and mood. Investigations into central nervous system androgen and estrogen receptors and their ubiquitous presence in both male and female brains suggest androgen’s role in normal female embryologic development (6). The question that continues to be debated is whether women can develop androgen insufficiency in their adult lives, either from intrinsic inadequacy of androgen production by the adrenals, ovaries, and other sources, or

TABLE 2**Androgen insufficiency.**

Reduced
 Sex motivation
 Sex fantasy
 Sex enjoyment
 Sex arousal
 Vaginal vasocongestion
 Pubic hair
 Bone mass
 Muscle mass
 Quality of life
 Mood
 Affect
 Energy
 More frequent
 Vasomotor symptoms
 Insomnia
 Depression
 Headache

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from elevated sex hormone-binding globulin (SHBG) associated with oral contraceptive pill use or estrogen replacement therapy (7). In the male, the majority of testosterone production occurs in the testes. In the female, 25% of testosterone is produced in the adrenals, 25% in the ovaries, and 50% in the peripheral tissues from prehormones produced in the adrenals and ovaries (6).

Data available regarding androgen insufficiency in the female usually link its development to either loss of ovarian tissue from surgery, chemotherapy or radiation therapy, or to a decline in ovarian function associated with the menopause. In these instances, the resultant loss of androgen production leading to the physical alterations and behavioral symptoms associated with hypoandrogenism may be referred to as a state of female androgen insufficiency. The most common alterations associated with low androgen levels in women include a decline in sexual functioning, such as decreased sexual motivation, fantasy, and enjoyment; diminished sexual arousal; decreased vaginal vasocongestion in response to erotic stimuli; loss of pubic and axillary hair; increased vasomotor flushing and insomnia at menopause; loss of bone and muscle mass; replacement of muscle with adipose tissue; increased prevalence of depression and headaches; and a diminution in quality of life. These alterations impact mood, affect, and energy (Table 2).

ANDROGEN INSUFFICIENCY AT-RISK WOMEN

Because of the pivotal role of the ovary, women who are the most likely to experience a decline in their androgen levels, which leads to the symptoms described previously, are women who are surgically menopausal (8). Women who experience a natural menopause transition with resultant atrophy of ovarian tissue may also have a significant decline in stromal androgen production, which can cause these symptoms (9). However, because some data suggest that circulating total testosterone does not change, and that the free testosterone index actually increases with the menopause transition, symptoms at this time would not be caused by declining androgen levels (10). That is, an androgen decline would not occur at the time of a natural menopause, but would occur many years after the menopausal transition in the older woman who has significant ovarian atrophy. With functional, ovulatory ovaries, it is difficult to postulate a clinical scenario in which androgen insufficiency would occur in the reproductive-aged female unless other circumstances are impacting on physiologic ovarian function, such as the use of oral contraceptive pills or gonadotropic releasing agonists, lactation, or anorexia nervosa. The fact that pharmacologic interventions, such as oral contraceptives containing a low-androgenic progestin or estrogen replacement therapy, are recommended as treatment options for the women with androgen excess underscores their abilities to substantially decrease free androgen levels (11).

Some evidence suggests, however, that hypoandrogenism can occur in premenopausal women who menstruate regularly and who are not receiving pharmacologic interventions that would affect androgen levels. When these women are investigated, many have been found to have intrinsically low levels of total and free plasma testosterone, as well as low levels of DHEAS (9–13).

ANDROGEN INSUFFICIENCY: PRESENTING COMPLAINTS OF PATIENTS

In the older, postmenopausal female, the most common presenting symptoms associated with androgen deficiency are loss of libido and diminished sexual desire. Most clinicians do not consider complaints of lack of motivation and flat mood as androgen-related, although these complaints may be more prevalent symptoms overall than sexual dysfunction. The wide spectrum of symptoms and signs, including bone loss and muscle wasting that may be associated with androgen insufficiency in postmenopausal women, cannot be overlooked. For example, loss of sexual desire alone has been reported to affect 10 to 15 million women, with the numbers of women with loss of motivation or diminished affect probably even higher (14). Depression is another prevalent disorder in both men and women.

Depression is twice as common in women than in men, however, and estrogen has been found to have both mood-elevating and antidepressant effects (15). Some studies suggest that the addition of testosterone to hormone therapy may act synergistically with estrogen in the treatment of some hormone-related depressions (16). In one double-blind, placebo-controlled study of 84 patients randomized to either placebo, estrogen, or estrogen plus testosterone implants, the women on combination therapy had a better response than estrogen alone, although the difference was not statistically significant (17). In another study by Sherwin et al., combined estrogen and testosterone was found to be statistically superior to estrogen alone in treating energy, well-being, and appetite (18).

ADDITION OF ANDROGEN TO HORMONE REPLACEMENT THERAPY

Because of the clear cause and effect relationship between loss of ovarian function in the menopausal woman and resultant declines in gonadal hormones, most of the data on androgen insufficiency in the female are in the cohort of surgically menopausal women who have been placed on hormone replacement therapy containing either estrogen, androgen, or a combination. The menopausal women studied are those who have had excluded nonhormonal etiologies for their sexual difficulties and who report nonrelief of symptoms despite adequate dosing of systemic hormone replacement therapy with estrogen \pm progestogen.

The major findings from these studies is that estrogen alone does not relieve all symptoms associated with gonadal hormone decline, and that many women benefit from the addition of androgen in an environment of sufficient estrogen. Two reasons why estrogen alone is often not sufficient are: oral estrogen increases SHBG, which decreases the amount of circulating free testosterone; and estrogen and androgen act independently of each other at both peripheral and central receptors (19–21).

In a study by Casson et al., estrogen replacement decreased DHEAS, DHEA, and testosterone (20). A 2 mg-dose of oral micronized estradiol increased SHBG levels 160%. The independent role of androgen in postmenopausal women has best been studied in oophorectomized women. Pivotal studies by Sherwin et al. reported the effects of androgen replacement on improving sexual motivation activities and quality of life in surgically menopausal women — effects that were not seen with estrogen replacement alone (22, 23). Recent work by Shifren et al. also demonstrated the effect of androgen delivered transdermally on sexual function and quality of life, as compared with placebo and estrogen alone, although not all results were statistically significant (24). Other studies, such as the classic study by Burger et al. similarly showed that women on estrogen implants alone reported poorer relief of menopausal symptoms, compared with the condition in which combined estrogen and androgen implants were administered (25, 26).

Increasing evidence supports the role of testosterone as the hormone of sexual drive in women, regardless of the route of delivery. Some data in normal menopausal women, however, have not shown a statistically significant improvement in sexual function with the administration of estrogen and androgen replacement as compared with estrogen alone (27, 28). It can be concluded that no effect of androgen replacement will be observed in an environment without adequate estrogen levels.

ANDROGENS: PHARMACOLOGIC INTERVENTION

Due to the potential adverse effects of diminished androgen, the issue of pharmacologic intervention with androgen replacement assumes significance in the female population with androgen insufficiency, especially in the postmenopausal age group. Two common problems, however, have been noted in clinical management: many clinicians are unaware of the signs and symptoms or the normal range of androgen levels in women; and a lack of interdisciplinary approaches exist among the many specialties that treat women with androgen disorders. Women frequently present to gynecologists for vasomotor symptoms and insomnia at the time of menopause, but may not talk with their clinicians about the affective symptoms that they are experiencing. Instead, the services of a psychiatrist or psychologist may be

sought. Also, if marital problems occur due to loss of sexual desire or motivation, a couple may seek the care of a marital or sex therapist. For other medical problems associated with androgen loss, such as fatigue or memory loss, the woman may be under the care of an internist or family practitioner. Finally, a dermatologist may be treating the woman for changes in hair and skin. This fragmentation may obscure the underlying cause of androgen insufficiency and can lead to poor medical management of the condition.

SUMMARY AND CONCLUSION

The implications of this overview are that: [1] additional clinical trials are needed that assess the role of androgens in women and the resultant clinical problems that occur as they decline with aging and the menopause; and [2] a coordinated team approach is needed in caring for women with symptoms linked to both hyperandrogenic and hypoandrogenic states (29). It is clear that androgens affect many organ systems of the body. In addition to quality-of-life and sexual outcomes, their impact on muscle, bone, cognitive function, and cardiovascular function should be better characterized.

Furthermore, education is needed on the role of androgens in women's health, not only in the medical community but in the general population. Many women consider androgens either a hormone exclusively important in males or associate their use with ingestion of supraphysiologic levels as reported among athletes. One group of patients who would clearly benefit from increased awareness of androgen's role in the female are surgically menopausal patients who experience abrupt losses of both estrogen and androgen in the operating room at the point that their ovaries are excised. Lastly, a better understanding of the role of androgens in premenopausal women is needed as scant data exist in this large cohort of women.

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