Androgens: Putting Sex Drive Back into Gear?

By John A. Lamont, MD, MSc, FRCSC

Joanne's lack of desire

Joanne, 37, is married and, at her annual well-woman examination, she asks for a prescription to stimulate her sexual desire. She has had no desire for over two years, since her first child was born. For six months post-partum she suffered from fatigue, depression and mastalgia. Early attempts at lovemaking were unsuccessful because she could not achieve arousal, and caressing irritated her.

At present, Joanne's husband works long hours, is frequently tired and avoids any physical intimacy. Joanne's mood continues to be irritable and she is resentful that there is no time for her relationship with her husband. She misses physical intimacy, and is worried that her marriage is being threatened. She would also like to have another child.

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1. **What is the importance of testosterone production in women?**
2. **How accurate is serum testosterone measurement?**
3. **What testosterone replacement is available for women?**

Loss of sexual desire occurs more frequently than any other sexual complaint. Dysphoria aging, fatigue, medication, and relationship conflict can contribute in their own way to this change. Reassurance, counselling, or couple therapy have been proposed as treatment for this problem.

The current interest in the use of testosterone in women with low sexual desire was stimulated by an Oprah Winfrey Show in September 1998.

Low Libido

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Talk show host Christina Ferreira told viewers she had lost interest in sex and feared for her marriage until Dr. Judith Reichman, a California gynecologist, gave her a prescription that revived her interest in sex. This prescription was a 2% testosterone ointment which had been in use for many years, by gynecologists, as a treatment for lichen sclerosis but not viewed as a therapy for low desire. Prior to this time, research suggested testosterone improved sexual interest and responsivity in premenopausal women who went through surgical menopause. Following the show, the response from premenopausal, post-menopausal, and surgically menopausal sexually distressed women was overwhelming.

What does the literature say?

Although early authors report improved sexual desire with testosterone supplements,[1] the first control trial was reported in 1950.[2] The literature since then is a collection of clinical reviews and reports which have not contributed to the development of the usual scientific underpinings needed to clarify the role of testosterone in women with low or lack of sexual interest.

A review of the literature reveals few randomized control trials, most written during the '80s.[2-8] The best study from this group was conducted by Sherwin and reported in 1985 involving surgically menopausal women.[8] The results of this study are supported by Shifren's recent study using a testosterone patch.[9] She confirmed testosterone replacement therapy is generally efficacious in young women whose testosterone levels have dropped following bilateral oophorectomy, but its role in premenopausal women is still controversial.

Dr. Lamont is professor emeritus, department of obstetrics and gynecology, faculty of health sciences, McMaster University, Hamilton, Ontario.

What is the importance of testosterone production in premenopausal women?

In premenopausal women, 25% of circulating testosterone comes from adrenal production, 25% from ovarian stroma, and 50% is produced at tissue sites in the periphery where adrenal precursors, such as androstenedione, are converted to testosterone. Testosterone production peaks at ovulation as does androstenedione.[10,11]

Over the reproductive years (20 to 50 years of age) there is a gradual decline of testosterone production by 50%. In post-menopausal women the ovarian stroma continues to produce testosterone. After surgical menopause, testosterone levels dropped by about 80% in premenopausal women and by about 50% in post-menopausal women.

A factor in the level of circulating testosterone is the presence of a carrier protein called sex hormone binding globulin (SHBG). Of clinical importance is the degree to which androgens are bound to this protein. Sixty-six per cent of testosterone is bound to SHBG and 32% is albumin bound. Only 2% of circulating testosterone is free. Bioavailable test is a combination of free and albumin bound testosterone. SHBG increases with age as the production of total testosterone gradually declines. Oral hormone therapies (oral contraceptives and oral estrogen

replacement therapy) stimulate SHBG production in the liver, resulting in a corresponding decline in free or bioavailable testosterone.

How accurate is serum testosterone measurement?

Measuring serum testosterone as part of an assessment of a woman complaining of low sexual desire can be problematic.[10,11] Different measurement techniques can yield markedly varying levels of free testosterone. The upper limits of normal range for women vary substantially between labs and measurements in the lower third of the normal range are notoriously inaccurate. Current expert opinion states that women most likely to respond to testosterone replacement therapy will have a serum-free testosterone in the lower third of the female reproductive range or below the lower limit of normal. In a recent review of our clinic, 56% of 500 consecutive referrals presented with complaints of low sexual desire or no sexual desire. Of these referrals, 91% were females with low desire. In persons with low or no sexual desire, these complaints are often accompanied by problems of arousal and orgasm.

Androgen insufficiency can be caused by hypopituitarism, Addison's disease, corticosteroid therapy, ovarian failure, and oophorectomy. Physiologic mechanisms to explain loss of desire accompanied by low free or bioavailable testosterone are not clear in most cases.

In 1993, Dr. Helen Singer Kaplan outlined her study of 11 women who she described as suffering from "the female androgen deficiency syndrome (FADS)."[13] She concluded that the loss of androgens in women is associated with a marked decrease in sexual desire or libido. This loss was accompanied by a decrease or absence of sexual fantasy and markedly decreased or absent sexual response and orgasm. In 2001, Lobo described relative androgen deficiency, a clinical syndrome related to androgen deficiency which included decreased energy and blunted motivation, flat mood, diminished well-being, irri-

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tability, insomnia, and decreased sexual desire or libido.[14] In 2002, Bachman et al reported that a "conservative definition of androgen insufficiency in women" included a diminished sense of well being or dysphoric mood, unexplained fatigue, sexual function changes (in particular loss of desire).[11] This group stated that the diagnosis could only be made in symptomatic women who are well-estrogenized and would have a free testosterone level at or below the lowest quartile of the normal range for the reproductive age group.

What therapy is available for women?

The use of androgens with or without estrogen in women to enhance sexual interest and function dates back to the '40s. At present, there are no formulations in Canada specifically for women. Oral, injectable, and transdermal treatments are prescribed "off label." Products available for men can be used in appropriate dosages to improve the circulating free testosterone in women with low testosterone and low desire. There is evidence to suggest that testosterone supplements work better in women who are well estrogenized and especially in younger women who have undergone bilateral oophorectomy.[8,14] Oral estrogen can, in fact, decrease circulating testosterone by stimulating the liver to produce more SHGB. If estrogen supplements are needed, the preferred choice would be a transdermal estrogen combined with either transdermal testosterone, oral testosterone, or injectable testosterone. Careful monitoring is necessary and includes a monthly review of benefits, side-effects and serum free testosterone with an adjustment of the dosage if indicated.

In our study, approximately 20% of women presenting with low or no sexual desire were assessed as appropriate for testosterone replacement. In those who completed a three-month trial, improvement in sexual interest and response was reported by 70% of women. The reactions ranged from "It's a miracle" to "My desire has been restored," although others reported they felt more receptive to sexual invitations from their partner or had more intense sexual response including improved lubrication, arousal or more fantasies ,and more intense orgasm. Most women also reported more energy and an improved sense of well-being.

On the negative side, 15% reported adverse side effects, including some acne and oily hair (in premenopausal women), hypersensitivity of the clitoris, weight gain (two to five pounds of muscle), dysphoria, irritability and aggressive behaviour (worsening premenstrual syndrome), and two women reported skin reactions to the transdermal testosterone. No irreversible side-effects were reported. It should be emphasized that careful monitoring is important. In all patients reporting adverse effects, their free testosterone level had crept above the upper limit of the normal physiologic range for women. Special counselling is required when using testosterone in pre-menopausal women because of the risk of pregnancy and the potential virilization of a female fetus. CME

Net Readings

1. http://www.natural-hrt.com/artman/publish/article_99.shtml
2. http://www.jeanhailes.org.au/health_prof/hp_htt_androgens.htm

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Take-home message

The role of androgens in women's health is not clearly understood and the scientific study of this subject has been generally neglected.

- The present management of women complaining of low desire and having a relative androgen deficiency relies on clinical observation and intervention trials that are not supported by large-scale epidemiologic reports.
- Surgically menopausal women, especially those who are premenopausal at the time of surgery, are the only women in which testosterone can be clearly shown to improve libido.
- Clinical experience suggests it may also be helpful in women who have a major problem with symptoms of androgen deficiency, and a low free testosterone level rather than psychosocial problems.

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