



## Clinical Update

### Androgen treatment in women

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MJA 1999; 170: 545-549

Many women, both before and after menopause, may have symptoms of androgen deficiency: unexplained fatigue, lack of well-being and diminished libido. If plasma levels of bioavailable testosterone are low, these symptoms will mostly be relieved by judicious administration of testosterone. The addition of testosterone to postmenopausal hormone replacement regimens is becoming more widespread, and other potential uses include prevention and treatment of bone loss, treatment of spontaneous or iatrogenic androgen deficiency in premenopausal women, and, possibly, management of the premenstrual syndrome.

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[Introduction](#) - [Physiological effects](#) - [Androgen deficiency](#) - [Measurement of](#) - [Clinical indications](#) - [Administering testosterone](#) -  
[Conclusions](#) - [References](#) - [Authors' details](#)  
[Register to be notified of new articles by e-mail](#) - [Current contents list](#) - [Articles on similar material](#)

#### Introduction

No longer can it be said that androgens make boys as boys, and oestrogens, girls as girls. It is now known that high levels of oestrogen in the male brain in early life are necessary for male sexual imprinting,<sup>1</sup> and that oestrogen has a fundamental role in spermatogenesis<sup>2</sup> and maintenance of bone mineralisation in men.<sup>3</sup> The reverse also applies. Androgens have important and varied physiological actions in women.

#### Physiological effects of androgens in women

During the reproductive years androgens are produced by the adrenal glands and the ovaries ([Figure](#)). Androgens act directly via the androgen receptor in tissues, such as bone, skin fibroblasts, hair follicles and sebaceous glands,<sup>4</sup> and also have a vital role as the precursor steroids for oestrogen biosynthesis in the ovaries and extragonadal sites, including bone, brain, cardiovascular and adipose tissues. Hence, maintenance of physiological circulating androgen levels is important for an adequate supply of substrate hormone for oestrogen production at these sites. The physiological significance of this is best exemplified by osteoporosis in men, with a mutation in the

aromatase enzyme gene which affects the conversion of androgens to oestrogens; oestrogen replacement increases bone mineral density.<sup>3</sup>

It seems well established that testosterone is an important determinant of female sexuality,<sup>5-9</sup> and that it has a physiological role in the development and maintenance of bone mineralisation.<sup>10,11</sup> Other aspects of testosterone action in women currently being investigated include variations in testosterone level during the menstrual cycle and the behavioural changes in the premenstrual syndrome,<sup>12</sup> as well as the effect of androgens on the immune response and autoimmune diseases.<sup>13,14</sup>

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## Androgen deficiency in women

The prevalence of "androgen deficiency" in women has never been systematically evaluated, and there is no consensus clinical definition of this condition in women. Furthermore, a biochemical definition of androgen deficiency has been hampered by the insensitivity of most testosterone assays at the lower end of the normal range in women in their reproductive years. Women most likely to respond to androgen therapy have the following features: low libido, blunted motivation, fatigue and lack of well-being, associated with normal plasma oestrogen levels and low levels of bioavailable testosterone.

Symptoms of "androgen deficiency" are often attributed to psychosocial and environmental factors, and many affected women, unaware that their problems may have a biological basis and apprehensive about the response such problems will elicit, often do not report them. Moreover, the basis of each of the symptoms listed above is likely to be multifactorial, making it important for treating physicians to evaluate and deal with other factors before considering androgen replacement.

In general, the concept of androgen deficiency has been most widely accepted for women who have had bilateral oophorectomy. However, women who have undergone a natural menopause not infrequently experience "androgen deficiency" symptoms, as do a subset of women in their late reproductive years. Young women who have suffered either primary or secondary ovarian failure may also experience low libido in association with low blood androgen levels.

A general approach to evaluating women with symptoms suggestive of androgen deficiency, as well as the possible causes of androgen deficiency, are outlined in [Boxes 1](#) and [2](#), respectively.

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## Measurement of androgen level

Before commencing testosterone therapy in any woman, levels of testosterone and sex hormone binding globulin (SHBG), and the free androgen index (calculated to adjust for variations in SHBG), should be evaluated. Low bioavailability of testosterone is indicated by either a low ratio of levels of total testosterone to SHBG, or a free testosterone level in the lower third of the normal range in women in their reproductive

years.

A diagnosis of symptomatic androgen deficiency would be highly questionable with a total testosterone level in the upper third of the normal reproductive age range and a normal free androgen index. However, it is not uncommon for a midrange level of testosterone to be associated with androgen deficiency because of a very high SHBG level secondary to exogenous oestrogen replacement in postmenopausal women. Although DHEA-S and androstenedione are important precursors of testosterone, their measurement does not aid in diagnosis.

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## Clinical indications for androgen therapy in women

### Sexual dysfunction

There are multiple influences on libido and frequency and enjoyment of sexual activity in women. However, androgens appear to be important determinants of female sexuality and low circulating levels are associated with diminished libido. The relationship between androgens and the female sexual response has been reviewed recently.<sup>22</sup>

**Bilateral oophorectomy:** Anecdotal accounts suggest that the women most likely to respond to testosterone are those who have undergone bilateral oophorectomy.

**Premature menopause:** Testosterone replacement should also be considered part of the management of young women with premature menopause, particularly those with Turner's syndrome (45,XO). In general, women who undergo menopause in their reproductive prime suffer considerably from symptoms related to androgen deficiency, particularly diminished libido. Alternatively, young women with premature menopause who have not previously been sexually active should be made fully aware of the availability of androgen replacement and, in some instances, offered low dose androgen therapy as part of their hormone replacement.

**Premenopausal women:** It is not uncommon for premenopausal women to complain of diminished libido, and, when other potential influences on sexual dysfunction can be excluded and they have low levels of bioavailable testosterone, androgen replacement therapy is likely to be beneficial.

**Postmenopausal women:** Most women do not report loss of sexual desire after spontaneous menopause, but there is generally an age-related reduction in sexual frequency associated with the menopausal transition.<sup>23</sup> In a study of sexagenarian women, the only hormone to positively correlate with sexual desire was circulating free testosterone.<sup>9</sup> Although oestrogen replacement improves vasomotor symptoms, such as vaginal dryness and possibly general well-being, it has little effect on libido.<sup>24</sup> In contrast, the addition of testosterone to a hormone replacement regimen results in improvement in several aspects of sexuality in postmenopausal women.<sup>5-7,25</sup>

As a general rule, testosterone replacement should not be administered to postmenopausal women who are not taking concurrent oestrogen replacement. Oestrogen alone may relieve other postmenopausal symptoms, alleviate vaginal dryness and enhance sexuality, obviating the need for androgen therapy. Furthermore, suppression of SHBG with testosterone alone may increase the possibility of adverse side effects. The only exception to this rule is the use of nandrolone decanoate (see below) in postmenopausal women for the prevention of osteoporosis.

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## Prevention and treatment of bone loss

### In premenopausal women:

- Bone loss (particularly in the hip) is associated with low total and free testosterone levels.<sup>11</sup>
- Increased circulating androgen levels are associated with higher bone mineral densities.<sup>26</sup>

### In postmenopausal women:

- Low circulating free testosterone is predictive of subsequent height loss (a surrogate marker of vertebral compression fracture), and hip fracture.<sup>27,28</sup>
- Treatment with either oral or parenteral oestrogen-plus-testosterone therapy results in beneficial effects on bone mineral density over and above those seen with oestrogen alone.<sup>22,29</sup>
- Oral esterified oestrogen with methyltestosterone not only increases spinal bone mineral density but also suppresses biochemical markers of bone resorption, with an increase in markers of bone formation over two years.<sup>30</sup>
- Circulating levels of DHEA and DHEA-S are positively correlated with bone mineral density in older women.<sup>31,32</sup>
- The daily application of a 10% DHEA cream resulted in an increase in bone mineral density of the hip in older women.<sup>33</sup>

As yet, no studies have addressed the impact of androgen therapy on fracture incidence, although the effects of androgens on the mechanical properties of bone have been studied in female cynomolgus monkeys:<sup>34</sup> testosterone therapy resulted in increases in intrinsic bone strength and resistance to mechanical stress, as well as increases in bone mineral density, bone torsional rigidity and bending stiffness.<sup>34</sup>

Potential and more controversial uses for androgen therapy are described in [Box 3](#).

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## Administering testosterone to women

**Availability:** Testosterone has been available as oral methyltestosterone on prescription in North America for many years, and testosterone implants were approved for replacement therapy in postmenopausal women in the United Kingdom in the early

1990s. These and all other available testosterone preparations have primarily been formulated for use in men. Currently, the use of testosterone for hormone therapy in women is not approved in Australia. Despite the lack of approval, specialist menopause clinics in Australia have had more than a decade of experience of testosterone use in menopausal women, and hence management advice based on clinical experience is available.

**Nandrolone decanoate:** Nandrolone decanoate (Deca-Durabolin, Organon) is a very weak aromatisable androgen, available in Australia on authority for treating postmenopausal osteoporosis, and administered intramuscularly. The dose should not exceed 50 mg, with the frequency of administration being titrated against the patient's build (ie, it is recommended that it is given 6 weekly, but 8-12 weekly in women with a body mass index lower than 20 kg/m<sup>2</sup><sup>2</sup>, otherwise virilising effects such as hirsutism and voice deepening are not uncommon). This drug will result in cessation of bone loss in most older postmenopausal women and, in some women, in an absolute increase in bone mineral density. When given 6-8 weekly this therapy does not usually improve libido.

**Testosterone implants:** Women experiencing diminished libido are usually treated with testosterone implants and, less commonly, with mixed testosterone esters. Subcutaneous testosterone pellet implants (fused crystalline implants 4.5 mm in diameter) are the most common form of androgen therapy in women in Australia. The implant is usually inserted subcutaneously in the lower anterior abdominal wall under local anaesthesia using a trochar and cannula. A dose of 50 mg, obtained from a 100 mg implant, is extremely effective in enhancing libido and improving bone mineral density without generating unwanted virilising side effects.<sup>7,22</sup> It is usually effective for between three and six months, but, because of marked individual variation, testosterone levels should be measured before each subsequent implant is inserted. Rarely are testosterone implants of 100 mg necessary to achieve adequate clinical effects. Indeed, circulating testosterone levels about three times the upper limit of normal have been reported four weeks after insertion of a 100 mg testosterone pellet,<sup>40</sup> and six weeks after insertion of a 50 mg implant mean circulating testosterone levels were just above the upper limit of normal for ovulating women.<sup>22</sup> A 100 mg dose may be needed in young women with premature ovarian failure or after early oophorectomy.

**Mixed testosterone esters:** Although there are no published studies to support their use in women, mixed testosterone esters 50-100 mg (Sustanon, Organon) are occasionally administered 4-6 weekly as an intramuscular injection to women with androgen-deficiency symptoms. Anecdotally, this therapy results in a much more rapid onset of effects; women report enhanced libido after 2-3 days of treatment, compared with after 7-10 days with testosterone implants. The pharmacokinetics of mixed testosterone esters in women have not been studied, but women more commonly report an increase in acne and other virilising effects due to apparent peaks in testosterone levels after injection.

**Transdermal testosterone matrix patch:** A transdermal testosterone matrix patch intended specifically for use in women has been developed and is currently undergoing

early clinical trials. The patch is designed to deliver 150 µg of testosterone per day with twice-weekly application, resulting in an average increase in circulating testosterone levels of about 1 nmol/L.

For more information see [Box 4](#)

#### Adverse effects

Clinical experience suggests that, to achieve a good response in terms of libido, the testosterone level often needs to be restored to at least the upper end of the normal physiological range in young ovulating women. However, the dose needs to be titrated to keep circulating testosterone close to physiological levels to avoid adverse masculinising effects.

Side effects of testosterone in women are rare when the hormone is appropriately administered. However, with excessive dosage, virilisation and fluid retention may occur. Potentially adverse lipoprotein-lipid effects (eg, reductions in high density lipoprotein cholesterol and apolipoprotein A1 levels) may occur with excessive oral administration, but have not been reported with parenteral therapy.<sup>22</sup> Clinical data to hand do not indicate that testosterone therapy, with testosterone levels kept close to and within the normal physiological range for women, has any undesirable metabolic consequences.<sup>22,41</sup> It is not known whether there is any relationship between exogenous androgen therapy and the incidence of breast cancer, as epidemiological studies have shown both positive and negative associations between endogenous androgen levels and risk of breast cancer. Androgen receptors are found in over 50% of breast tumours,<sup>42</sup> and are associated with longer survival in women with operable breast cancer and a favourable response to hormone treatment in advanced disease.<sup>43</sup> There are also some data to suggest that the therapeutic effect of high dose medroxyprogesterone acetate on breast cancer is mediated via the androgen receptor.<sup>44</sup>

#### Contraindications

Pregnancy and lactation, as well as known or suspected androgen-dependent neoplasia, are absolute contraindications to testosterone therapy. Relative contraindications include moderate to severe acne, hirsutism, androgenic alopecia and any circumstance in which enhancement of libido would be undesirable.

It is now recognised that the treatment of the postmenopausal woman with testosterone replacement may result in an ethical dilemma if the woman is a participant in older-age competitive sport. This is a controversial issue that is yet to be resolved.

#### Conclusions

Women reporting loss of libido may find physicians insufficiently empathetic, and a biological cause for sexual dysfunction in women is rarely sought. However, it is gradually becoming more accepted that androgen deficiency in women may underpin a variety of symptoms and pathophysiological conditions and that, in selected women, androgen replacement therapy is of clinical benefit.

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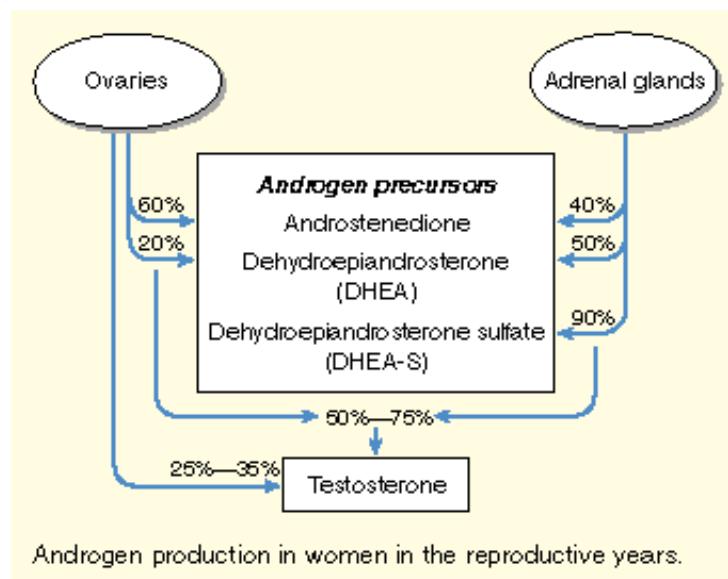
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[Back to text](#)

## 1: Evaluation of androgen deficiency in women

### Clinical suspicion of androgen deficiency

- Gradual loss of sexual desire in otherwise satisfying sexual relationship
- Persistent fatigue with no clear cause
- Premature ovarian failure
- Bilateral oophorectomy

### Exclusion of other causes of symptoms

- Full psychosocial history
- Assess adequacy of oestrogen therapy in postmenopausal women
- Exclude other causes of fatigue (eg, iron deficiency, hypothyroidism)

### Tests to establish androgen deficiency

- Total testosterone level
- Sex hormone binding globulin (SHBG) level
- Free androgen index
- Dehydroepiandrosterone-sulfate (DHEA-S) level

## Consider androgen therapy for women with:

- Symptomatic testosterone deficiency after natural menopause
- Symptomatic testosterone deficiency following oophorectomy, chemotherapy or radiotherapy
- Premature ovarian failure -- primary or secondary
- Premenopausal loss of libido with low level of bioavailable testosterone.

[Back to text](#)

## 2: Causes of androgen deficiency in women

### Age-related

- Physiological circulating androgen levels (total and free testosterone, dehydroepiandrosterone [DHEA], and dehydroepiandrosterone-sulfate [DHEA-S]) fall continuously with age,<sup>15,16</sup> commencing in the decade preceding the average age of natural menopause. This is a consequence of the concurrent decline with age in adrenal production of the preandrogens DHEA, DHEA-S and androstenedione, and diminished testosterone production by the ovaries.<sup>16,17</sup>

### Iatrogenic

- Oophorectomy -- bilateral oophorectomy results in a 50% fall in testosterone and androstenedione. Chemical oophorectomy results from administration of gonadotropin-releasing hormone antagonists, chemotherapy or radiotherapy.
- Administration of exogenous oestrogen -- combined oral contraceptive pill or oral postmenopausal oestrogen therapy increases sex hormone binding globulin (SHBG) levels (thus reducing free testosterone), and suppresses pituitary luteinising hormone production (hence lessening stimulation of ovarian androgen biosynthesis).<sup>18,19</sup>
- Administration of exogenous glucocorticosteroids -- glucocorticosteroids reduce adrenal androgen production by suppressing ACTH.<sup>20</sup> This appears to contribute to the pathogenesis of osteopenia and osteoporosis, the side effects of long term glucocorticosteroid therapy.

### Pathological

- Hypothalamic amenorrhoea or hyperprolactinaemia in

premenopausal women.

- Premature primary or secondary ovarian failure. Bone loss complicates each of these conditions and appears to progress despite adequate oestrogen-progestin therapy.<sup>21</sup> Young women with these conditions may also require testosterone replacement to prevent progressive bone resorption.

[Back to text](#)

### 3: Potential indications for androgen use in women

- **Postmenopausal loss of muscle mass:** In postmenopausal women testosterone therapy is associated with an increase in fat-free mass and a reduction in the fat mass to fat-free mass ratio.<sup>22</sup> As this gain in fat-free mass probably reflects increased muscle mass, and ageing is associated with loss of muscle mass, testosterone therapy is beneficial in older women.
- **Management of wasting in HIV infection:** Testosterone levels are lower in HIV-positive premenopausal women.<sup>35</sup> Augmentation of testosterone levels with a transdermal testosterone patch is associated with increased mean body weight and body mass index as well as improved quality of life.<sup>36</sup>
- **Testosterone and the premenstrual syndrome:** Significantly lower levels of testosterone throughout the menstrual cycle have been reported in women who suffer premenstrual syndrome compared with controls.<sup>12,37</sup> Testosterone is being used in selected patients with premenstrual syndrome in specialised centres in the United Kingdom and Australia, and randomised trials evaluating the effects are under way.
- **Testosterone and autoimmune disease:** Sex differences in the pattern of autoimmune disease are well recognised, and may be related to higher testosterone levels in men, with some studies indicating that androgens suppress both cell-mediated and humeral immune responses.<sup>14,38</sup> Reports in postmenopausal women with rheumatoid arthritis indicate symptomatic improvement with testosterone replacement,<sup>13</sup> and reductions in disease activity with DHEA therapy.<sup>39</sup> However, apart from its use to counteract the side effects of long term glucocorticosteroid therapy (muscle wasting and bone loss) in autoimmune disease, much more substantial evidence is required before testosterone can be advocated as

adjunctive therapy in autoimmune diseases.

[Back to text](#)

#### 4: Prescribing androgen replacement

##### **Nandrolone decanoate**

Approved for use in postmenopausal women with osteoporosis, on authority

Dose range:	25-50 mg
Route:	Intramuscular
Frequency:	6-12 weekly

##### **Testosterone implants**

Approved for use in women in the UK, but not in Australia

Dose range:	50 mg (rarely, 100 mg)
Route:	Subcutaneous
Frequency:	3-6 monthly

##### **Mixed testosterone esters**

Not approved for use in women. No published data pertaining to use in women

Dose range:	50-100 mg
Route:	Intramuscular
Frequency:	4-6 weekly

##### **Testosterone undecanoate**

Limited data in women indicate high circulating peak levels.  
Not approved for use in women

Dose range:	40 mg
Route:	Oral
Frequency:	Alternate days/daily

##### **Methyltestosterone**

In combination with esterified oestrogen, approved for women in USA

Dose range:	1.25-2.5 mg
Route:	Transdermal
Frequency:	Daily

**Transdermal testosterone matrix patch**

Undergoing clinical trial

Dose range:	150 $\mu$ g
Route:	Transdermal
Frequency:	Changed twice weekly

[Back to text](#)