

Testosterone and androgens in women

<http://womenshealth.med.monash.edu.au>

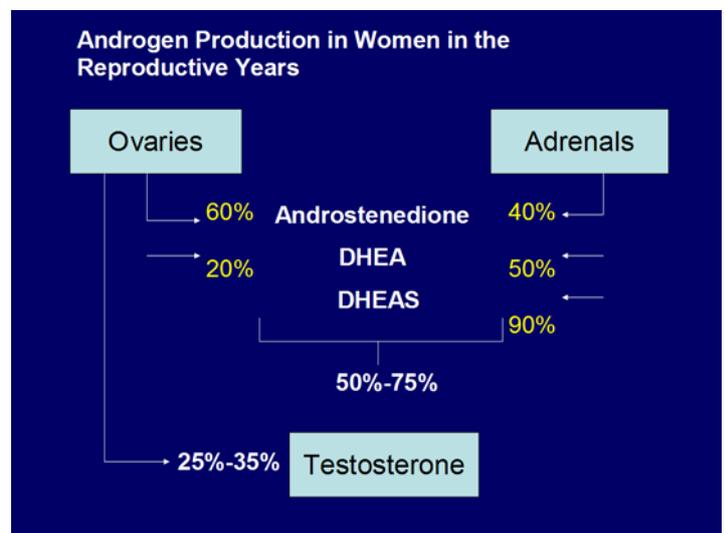
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1. Women normally produce testosterone:

Androgens are sex hormones produced by both the ovaries and the adrenal glands in women and by the testes in men. They are known mostly for their masculinising effects in men, namely, beard growth, deeper voice, balding, muscle strength and potency. The main androgens in women are the adrenal androgens and testosterone. In women, fifty per cent of testosterone is produced by the ovaries and adrenal glands and released directly into the blood stream.

Testosterone is a hormone that is important in both women and men, with the difference being that men make significantly more testosterone than women.

In young women, testosterone is made primarily by the ovaries along with oestrogen and progesterone. Testosterone is also produced in other body tissues such as body fat and skin by conversion of hormones produced by the adrenal glands called dehydroepiandrosterone (DHEA) and DHEA sulphate (DHEAS) and **androstenedione** from the ovaries.



The ovaries make oestrogen by converting testosterone to oestrogen. After menopause, when the ovaries no longer do this, female fat tissue is the main source of estrogen which is made by converting adrenal androgens to weaker oestrogens in the fat. Testosterone and other related hormones in the body (DHEA/DHEAS) have important physiological roles in women.

How testosterone acts:

Oestrogen is made from testosterone and the other adrenal hormones and without the ability of our bodies to make testosterone we cannot make oestrogen.

Therefore an important role of testosterone is to provide the basic structure for oestrogen production

Testosterone has direct independent effects on the *androgen receptor* in different parts of the body, and some women may experience a variety of physical symptoms that could possibly be related to testosterone actions.



Very little testosterone circulates freely in the blood stream. Instead 66 per cent of testosterone is bound tightly to a protein known as sex hormone binding globulin (SHBG) and 33 per cent is bound to the important blood protein called albumin.

Therefore only about one to two per cent of testosterone circulates in the blood of young healthy women free or not bound to a protein.

This is important when considering testosterone excess and testosterone deficiency.

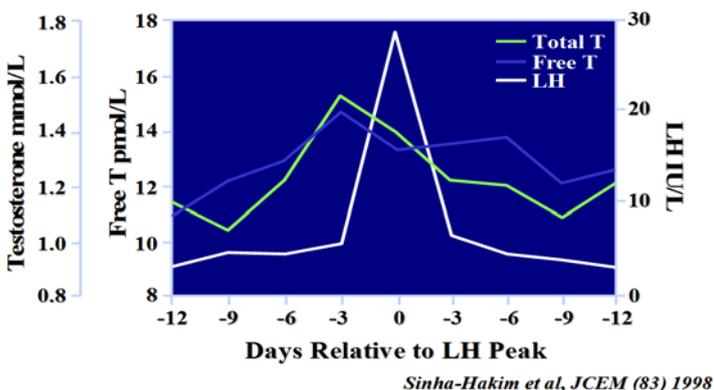
- Factors which lower SHBG will result in more free testosterone circulating and therefore women with lower SHBG levels are more likely to be masculinised with hairiness or acne.
- Factors which increase SHBG will result in more testosterone being bound up and less being free. Oestrogen therapy, either as the oral contraceptive pill or hormone therapy increases SHBG, resulting in reduced free testosterone and may cause lessened sexual desire and libido as a side effect.

2. Changes in testosterone over the normal menstrual cycle

Testosterone levels vary during the menstrual cycle just like other sex hormones, with testosterone peaking during the middle phase of the menstrual cycle around the time of ovulation. Some believe this may be an inbuilt stimulus to increased sexual activity in women close to ovulation and therefore nature's way of enhancing sexual activity close to ovulation and therefore increasing the likelihood of conception.

Testosterone levels are also higher in women in the morning than later in the day.

Mean levels of total and free testosterone and LH in blood during the normal menstrual cycle.



3. Changes in testosterone with age in healthy women

Aging affects female androgen production by two different mechanisms.

1. With increasing age the adrenal glands produce progressively less DHEA and DHEAS which are important sources of oestrogen and testosterone in women.

Why this happens is not known nor are the specific effects of the decline in DHEA well understood. There has been considerable interest in DHEA as an anti-aging therapy.

2. Testosterone levels decline with age most likely due to reduced ovarian production and lessened adrenal function.

- The fall in testosterone happens gradually before menopause; and
- Testosterone levels do not change over the time of natural menopause.

This contrasts with the sudden drop in oestrogen at menopause.

Testosterone levels in women in their 40s are about half those of women in their 20s.

Therefore the testosterone level of a 45 year old woman may well be in the 'normal range' for her age but still be much lower than what she has been used to in the past.

Women who have their ovaries surgically removed experience a sudden drop in blood testosterone levels of the order of 40–50 per cent.

This may or may not be associated with symptoms, particularly reduced sexual desire arousal and responsiveness despite oestrogen therapy. Testosterone treatment may be beneficial for some women who have had their ovaries surgically removed and who experience significant symptoms in the form of loss of libido and diminished wellbeing.

Testosterone therapy will not be the treatment answer for someone who has a poor partner relationship, depression or poor wellbeing due to other causes.

Women should also have thyroid disease and iron deficiency excluded as possible causes of their symptoms by having a blood test for these conditions.

4. Measuring testosterone and other androgens

There is no set level of testosterone or DHEA (usually measured as DHEA sulphate [DHEAS]) below which a woman can be said to be deficient but it is essential that women with normal or high levels are not misdiagnosed and treated as though they have insufficient testosterone. Levels of all the androgens decline significantly with age in normal healthy women, so a normal level for a 20 year old is most likely a high level for a 50 year old.

Most methods for measuring testosterone are fairly imprecise and become even more inaccurate when blood levels of testosterone are low. Measurement of DHEAS and SHBG are straight-forward.

When to measure testosterone:

Ideally blood should be taken between 8 am and 10 am as testosterone levels vary throughout the day. For women who have regular cycles, blood should not be taken during the menstrual phase as testosterone levels are low at this time in most women and thus the result may be misleading. Thus blood should be drawn at least eight days after the start of menstruation.

What can be measured:

Free or bioavailable (non-SHBG-bound) testosterone measures are thought to provide the best indication of what the cells are exposed to. However as testosterone can actually be made within cells without ever appearing as testosterone in the blood stream, measuring low blood free testosterone does not actually mean that there is low testosterone within cells. Levels of testosterone above average probably rules out symptoms being due to androgen insufficiency.

Free testosterone:

The gold standard method for measurement of free testosterone is considered by many investigators to be by 'equilibrium dialysis'. However, this method is labor intensive and expensive, and not feasible for routine use and clinical practice. This method also only estimates what *per centage* of testosterone is free. So, total testosterone also needs to be accurately measured so that the actual amount of free testosterone in the blood can be calculated.

Several groups have now shown that if total testosterone is measured accurately along with SHBG and albumin is normal, an equation called the **Sodergard equation** can be used to calculate free testosterone with high precision.

Measurement of free testosterone by analogue (kit) assays is notoriously unreliable and should not be used to assess testosterone in women.

The free androgen index (FAI) [$\text{nmol/L total testosterone} \times 100 / \text{nmol/L SHBG}$] has been used as a surrogate for free testosterone, but it is unreliable when SHBG levels are low.

Bioavailable testosterone, which correlates highly with free testosterone quantified by equilibrium dialysis, can be measured by the ammonium sulfate precipitation technique. However sources of error there are also frequently encountered in this method.

Salivary testosterone has been used in some studies of women with excessively high testosterone levels (hyperandrogenism). It is not useful diagnostically as the variability in normal healthy women is excessively wide and accuracy has been questioned. It is important to realize that salivary testosterone levels should not be equated to levels of free testosterone in serum.

Total testosterone: No rapid, simple assay of total testosterone has been shown to produce reliable results in women with low testosterone levels.

Direct automated kit testosterone immunoassays are limited by "noise" from assay interference and by cross-reactivity with other steroids, which becomes worse at low testosterone concentrations. Furthermore, testosterone is sometimes not completely dissociated from SHBG in a direct assay.

Measurement of total testosterone after organic solvent extraction will increase specificity, and if combined with chromatographic separation of testosterone from interfering steroids, a reliable result can be obtained. However, this technique is frequently not available or cost-effective in clinical settings.

Gas chromatography combined with mass spectrometry (GC-MS) for total testosterone measurement requires multiple steps including liquid-liquid extraction, and may not be reliable when testosterone levels are very low. However, liquid chromatography (LC)-MS/MS appears to provide reliable measurement of low testosterone concentrations.

Regardless of which assay method is used for measuring testosterone, a thorough validation of each method is required. The validation should include assay sensitivity, precision, accuracy and specificity.

Sex hormone binding globulin (SHBG) needs to be measured to fully understand a woman's androgen profile. SHBG binds with high affinity to testosterone and is an important regulator of the circulating total testosterone concentration. Having a low SHBG will enable free testosterone to clear easily into the cells.

The measurement of SHBG is not controversial and is relatively simple to perform with good reproducibility. Low SHBG levels may indicate an increase in risk of androgen excess with testosterone therapy where as very high SHBG may make a woman more resistant to the effects of androgen therapy.

Recommendations as to what to measure in clinical practice:

Total testosterone should be measured by the best available assay along with SHBG.

If possible free testosterone should be provided by the lab as a calculated free testosterone or free androgen index can be calculated.

There is no level of free testosterone or total testosterone that defines androgen deficiency. However, women with testosterone levels at the higher end of the normal range for young women might be more likely to have another cause for the symptoms and additional testosterone may result in side effects.

Once a woman is treated with testosterone it is important to monitor levels to ensure that she is not receiving excessive amounts of therapy.

Women with a low SHBG will be more at risk of adverse effects with testosterone therapy (higher free Te) and women with very high levels ($>160\text{nmol/L}$) are less likely to benefit from transdermal therapy.

Measurement of DHEAS: DHEA is usually measured in the sulphated form, DHEAS, because the half-life is much longer, resulting in more stable levels. The immunoassay for DHEAS is relatively stable, gives consistent results, and is simple to perform

DHEAS does not vary in concentration across the different phases of the menstrual cycle, and is not bound to SHBG. It also does not seem to be affected by estrogen therapy at standard doses.

If very low levels are found, a morning cortisol level should be drawn to rule out adrenal insufficiency.

5. Is there such a thing as female androgen deficiency?

Androgen deficiency has been described as a 'new clinical syndrome' despite the fact that some doctors have been treating women who have had their ovaries surgically removed with androgens for decades.

There are no defined levels of testosterone or DHEAS below which a woman can be diagnosed as androgen deficient. The lower limit of 'normal' has not been established for testosterone or DHEA. In contrast, several studies have shown that testosterone therapy improves sexual satisfaction and wellbeing in women presenting with these symptoms who are otherwise well.

Research undertaken within our NHMRC-funded Centre of Clinical Research Excellence for the Study of Women's Health have documented hormone levels in women recruited from the community and the same women have completed sexual satisfaction questionnaires. We sought to establish whether women who had very low scores on the sexual function questionnaires were more likely than other women to have low testosterone levels.

Our research did not reveal any relationship between having low sexual function scores and low testosterone. However women with low sexual function were three to four times more likely to have a DHEAS level in the lowest 10 per cent for their age.

These findings reflect the large amount of DHEAS in the blood (1000 x the concentration of testosterone in women) and the important role DHEAS has as the basic structure from which testosterone and oestrogen can be made within cells.

These findings do not mean that women with low libido should be treated with DHEA and not testosterone. Indeed there is very little research evidence to support that DHEA is effective therapy for low libido and there is almost no information regarding the safety of DHEA. **The findings do indicate that sex hormones are important for female sexual function and that simply measuring one level in the blood does not reveal all.**

In summary

There is no single blood test that can be used to make the diagnosis that a woman has androgen deficiency.

Several studies have demonstrated improved sexual satisfaction and wellbeing in both premenopausal and postmenopausal women treated with testosterone. The studies in postmenopausal women have involved both surgically and naturally menopausal women.

6. How to decide when to trial testosterone therapy

A variety of testosterone preparations are currently being used in clinical practice or in investigational research protocols for the treatment of sexual problems in women. In some cases testosterone products for men are used off-label at lower doses – this is a dangerous practice as the levels achieved are often much too high for women.

Testosterone therapy for women is available in Australia most readily in the form of testosterone implants and a testosterone transdermal (skin) cream. No form of oral testosterone has been designed for or approved for use in women in Australia although methyltestosterone can be prescribed in combination with oestrogen in USA.

Testosterone injections used for androgen replacement in men are sometimes given to women but there have been no studies addressing the use of this form of treatment in women and little is known about the suitable dosage, safety or efficacy of testosterone when given to women in this format. Testosterone injections result in very high blood levels of testosterone. As a result some women experience agitation, more aggressive moods and increased sexual thoughts which are sometimes reported as being unpleasant.

Testosterone implants (pellets) are approved for the treatment of women in the United Kingdom and parts of Europe and although not officially approved for this indication in Australia, they are in common usage. There is a body of scientific data demonstrating the short term (up to two years) safety of implants, but no longer term studies have yet been done. Usually testosterone implants are inserted under the skin in the lower abdomen using a simple procedure with oestrogen implants which are used by many women as an alternative mode of oestrogen replacement therapy. Oestrogen implants are approved for in women in Australia. When combined with oestrogen implants, testosterone implant therapy has been shown to significantly enhance sexual activity, satisfaction, pleasure, fantasy and orgasm in postmenopausal women.

A testosterone one per cent cream has been approved for use in women in Western Australia. It is measured out on a plastic spatula and approximately one to two cm is applied daily to the skin of the lower body. Blood levels must be monitored throughout the duration of use, initially after three weeks then three to six monthly. Two short term studies of this cream has shown efficacy is both premenopausal and postmenopausal women.

A transdermal testosterone skin patch which delivers 300 micrograms of testosterone to the circulation per day has been approved in Europe for the treatment of women who have undergone a surgical menopause (both ovaries surgically removed) and who have persistent loss of sexual desire despite adequate oestrogen therapy.

Currently transdermal testosterone in the form of a gel and skin spray are undergoing research. As yet none of these formulations are available for use in women in any country.

Research studies indicate that when women are treated with transdermal testosterone in a dose that brings blood levels into the normal range for young women, it takes about eight to 12 weeks before a clear improvement is achieved. Therefore any woman embarking on this therapy needs to understand that she must stick to the treatment for eight to 12 weeks before deciding whether or not she is going to benefit.

If no benefit is achieved by six months of therapy then there is no point continuing treatment.

Some pharmacies 'compound' individual prescriptions for testosterone, but the doses used are not based on any systematic research and the formulations have never been subjected to the most basic testing required for drug registration. There is no evidence of any safety data for compounded testosterone.

Women may be candidates for a trial of testosterone therapy if the report a decline in libido and sexual responsiveness after the age of about 35 year, post removal of ovaries or cancer therapy, adrenal gland failure or long term use of glucocorticosteroids therapy.

All women should be fully evaluated for depression as a cause of their loss of libido and relationship issues must be thoroughly explored. In addition, other factors that might negatively impact on sexual desire need to be excluded including past sexual abuse and concerns about sexual behaviour. Painful intercourse and vaginal dryness need to be evaluated and managed before testosterone therapy is considered.

Women should have routinely measured:

- iron stores (which might be low despite normal hemoglobin);
- thyroid stimulating hormone (TSH) to exclude subclinical thyroid disease;
- on clinical suspicion a screen for autoimmune disease causing chronic fatigue;
- Measurement of estradiol and FSH - to diagnose premature ovarian failure in amenorrhoeic young women or to evaluate menopausal status in hysterectomised women; and
- Prolactin should be measured in premenopausal women with oligomenorrhea, amenorrhea and/or galactorrhea.

7. Is testosterone therapy for women safe?

Testosterone has been widely used by women as an unapproved therapy for decades with an estimated two million prescriptions written for women in the US in 2006 and 2007. There are valid concerns regarding the use of testosterone therapy in women primarily when testosterone is used to excess. Virilisation is a deterrent to abuse, however abuse may put women at increased risk of cardiovascular disease, sleep apnea and aggressive mood change. Safety information regarding testosterone use in women is limited to short term use (less than two years), although many women in the community have been using testosterone therapy for many years.

Based on data to hand however, there is no evidence that non oral testosterone therapy that restores free testosterone levels to within, and not above, what is believed to be the range for women of reproductive age, in the setting of oestrogenisation (as endogenous production or concurrent exogenous oestrogen therapy) is associated with any adverse effects.

Twelve month data from the longest study of the testosterone patch conducted in Europe, Australia and USA does not indicate any serious side effects of this treatment in otherwise well women. The very long term effects of testosterone treatment (ie effects after five to 10 years) are not known.

Side effects and safety depend upon the dose administered, hormone levels achieved, the duration of treatment and the route of administration.

Masculinisation:

Long term use of excess doses will result in virilization: temporal balding, voice deepening, and clitoral enlargement. Other symptoms associated with exogenous androgen excess include hirsutism, acne, menstrual disturbances (in premenopausal women) and polycythemia. Although not well documented, genital application of topical androgens may cause clitoral enlargement.

Transdermal administration of testosterone at doses comparable to premenopausal hormone production has not been associated with virilization.

Cardiovascular risk:

There is no evidence that non oral testosterone therapy (patch, implants, gels etc) has adverse cardiovascular effects.

At conventional doses for women, oral methyltestosterone reduces the levels of HDL-cholesterol (the “good” cholesterol) and other liver proteins, including SHBG, TBG and CBG.

Liver:

High doses of orally administered methyltestosterone and possibly testosterone undecanoate may be associated with liver toxicity (peliosis hepatis, hepatic neoplasms and cholestatic jaundice) but this has not been a problem for lower dose therapy.

Risks in pregnancy:

In treating premenopausal women the risk of exogenous androgen to a fetus is a separate and genuine concern. However virilization of a female fetus does not appear to be tightly correlated with maternal testosterone levels, with the occurrence limited to women exhibiting masculinization. Nonetheless treatment of any women who have the potential to become pregnant should involve reliable contraception and extremely cautious monitoring.

Breast:

Two Australian studies have not shown any association between the use of testosterone implants or transdermal cream and increased breast cancer risk. However, despite a theoretical risk of testosterone therapy being its potential conversion to oestradiol, this has not been demonstrated. A recent small study conducted in Sweden suggests that testosterone may block some of the undesirable effects of oestrogen on breast cells when it is used by women taking postmenopausal oestrogen. Longer terms studies are needed before the effects of testosterone on the breast are well understood.