Androgens in women

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

Androgens are traditionally viewed as 'male' hormones, and in the context of women are usually only considered when there is concern about a woman having too many androgens, for example excessive hairiness and acne. But androgens are hormones of major physiological significance in women, being important for maintaining strong muscles and bones, positive protein balance, sexual desire and overall well being.

What are androgens?

Androgens are 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.

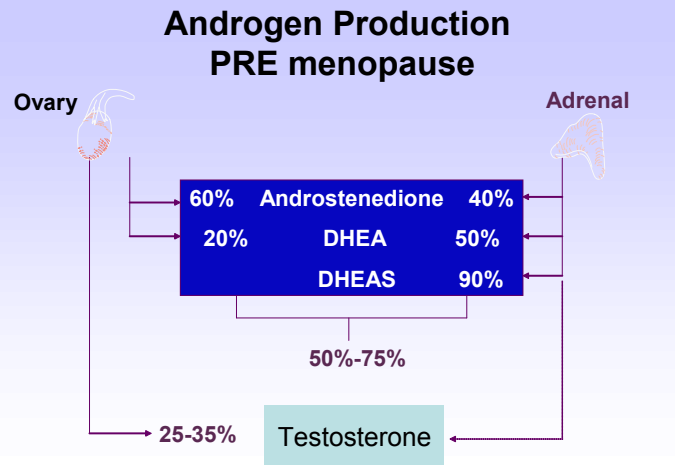
- In women, fifty per cent of testosterone is produced by the ovaries and adrenal glands and released directly into the blood stream. The other fifty per cent is made from conversion of the adrenal androgens to testosterone in other parts of the body.

The adrenal glands produce hormones we call "pre-androgens" as they are the main source of both testosterone and oestrogen production after menopause. In fact, the level of one of the adrenal pre-androgens known as DHEA-S in the blood stream is higher than any other human steroid except cholesterol. One of the critical roles for androgens in women is oestrogen production. Oestrogen is an end product of androgen metabolism.

- The ovaries make oestrogen by converting testosterone or DHEA to oestrogen.

After menopause, when the ovaries no longer do this, female fat tissue is the main source of oestrogen which is made by converting adrenal pre-androgens to weaker oestrogens in the fat.

Very little testosterone circulates freely in the blood stream. Instead 99 per cent of testosterone is bound tightly to a protein known as sex hormone binding globulin (SHBG). This is important when considering testosterone excess and testosterone deficiency. Factors which lower SHBG will result in more free testosterone circulating and therefore affected women are more likely to be masculinsed with hairiness or acne. In contrast, 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 replacement therapy increases SHBG, resulting in reduced free testosterone and may cause lessened sexual desire and libido as a side effect.



Davis 2005

Testosterone levels vary during the menstrual cycle just like other ovarian hormones, with testosterone peaking during the middle phase of the menstrual cycle around the time of ovulation. Some believe this may be an in built 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.

Changes in androgens with ageing

Aging affects female androgen production by two different mechanisms. With increasing age the adrenal glands produce progressively less androgens, specifically less DHEA, which are important sources of oestrogen and testosterone in elderly men and women. Why this happens is not known nor are the specific effects of the decline in DHEA well understood. There is however increasing interest in DHEA being an anti-aging therapy, as discussed below.

Menopause, which is unique to women, results in lessened ovarian androgen production, although this statement is somewhat controversial. The combined impact of ovarian failure at menopause and declining adrenal pre-androgen production with age is that older women have less testosterone circulating than young women. In the past, few people have been interested in this

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change, as already discussed, as it has been socially acceptable for older women to be less sexual. Awareness of the importance of androgens has been evoked by not only interested clinicians and researchers, but also by young women with androgen deficiency from either surgical removal of their ovaries or premature menopause and the vocal baby-boomer lobby who continue to demand quality of life.

Unlike oestrogen which falls precipitously at menopause, testosterone levels in women decline gradually such that women in their forties have blood testosterone levels which are on average half of those of women in their twenties. The testosterone level of a 45 year old woman complaining of low libido may well be in the 'normal range' for the test but still be much lower than what she has been used to in the past. Such a woman may well benefit in terms of libido and wellbeing by subtle testosterone therapy, still maintaining her levels in the 'normal range' rather than psychological treatment or anti depressant therapy.

Women who have their ovaries surgically removed experience a sudden drop in blood testosterone levels and commonly experience ongoing symptoms despite supposedly adequate hormone replacement therapy with oestrogen. Common symptoms include impaired sexual desire and function, lessened well being, loss of energy, depression and measurable loss of bone. As the absolute blood level of testosterone begins to decline in the decade preceeding menopause it is not surprising that many women experience similar symptoms in their premenopausal years. The cause of these symptoms is rarely recognised or understood, and virtually never treated.

Androgens and sexuality

There are significant associations between menopausal status and declining sexual activity and coital frequency. When women have been studied from their premenopausal through to their post menopausal years, specific patterns were observed. Mean weekly rates of sexual intercourse declined over the menopausal transition period. Compared with premenopause, the women after menopause had significantly fewer sexual thoughts or fantasies, experienced increased lack of vaginal lubrication during sex and were less satisfied with their partners as lovers. These changes were closely correlated with the decline in both oestrogen and testosterone with menopause however the fall in testosterone was most strongly associated with lessened coital frequency. Clearly the declining health and sexual interest as well as availability of a partner impacts on coital frequency, but this was not a significant factor in this study.

Furthermore, it has been suggested that lessened sexuality after menopause may be a self-fulfilling prophecy for some women, however the effect of anticipation of change in sexuality in women entering menopause has also been looked at, and the association between expectation of less sex and what is actually experienced is very weak.

In summary, there is increasing agreement that androgens play a key role in human female sexuality and that androgen deprivation after menopause contributes to a reduced sexual desire and responsiveness in a number of women. This aspect of adult female reproductive health is too often trivialised. Young women who suffer either premature menopause or who undergo surgical removal of both ovaries early in life commonly experience great distress from their loss of libido. It impinges on their intimate relationships and potential to develop new satisfactory sexual relationships and as one young women has said, results not only in loss of femininity, but of sexual 'personhood'. Such women are usually very responsive to testosterone therapy, and the significance of restoring sexuality to these women must not be over valued.

Our research does not show that women with low sexual interest are more likely to have low blood testosterone levels (published J *American Medical Association* 2005). However a number of studies have now shown that when women reporting low libido are treated with testosterone therapy (as an implant, gel, patch or tablet) there is an overall improvement in sexual interest and satisfaction in the treated women.

Unfortunately most of these studies have been short term ie 6–12 months duration. This is not long enough for us to be confident of the long term safety of testosterone therapy. Longer duration studies are currently under way.

Androgen therapy

Oestrogen therapy at menopause eliminates or lessens hot flushes, reverses vaginal dryness and hence improves lubrication with intercourse, and improves general wellbeing, but has little effect on libido. In contrast, androgen therapy using different formulations of testosterone, appears to enhance various parameters of sexual motivation including intensity of sexual drive, arousal and frequency of sexual fantasies not induced by oestrogen replacement alone.

Testosterone therapy for women does not have wide spread acceptance, particularly in North America, but is increasingly becoming more available as women demand acknowledgment of this aspect of their lives.

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 use 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 1 per cent cream has been approved for use in women in Western Australia. It is measured out on a plastic spatula and approximately one–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-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 twelve 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 twelve 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.

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 5 to 10 years) are not known.

Important points regarding testosterone therapy

- In general, testosterone therapy is not prescribed for postmenopausal women without oestrogen replacement simultaneously. However recent research indicates that testosterone without oestrogen therapy is not unsafe.
- When administered by testosterone implants, patch, cream or gel, blood testosterone levels should be measured at regular intervals to prevent overdosing and induction of undesirable masculinising side effects.
- Published studies have shown short term safety and efficacy of testosterone treatment by implants and skin patches in women
- There are no published studies addressing safety, dosage or efficacy of oral (tablet) testosterone treatment in women and until such time, this form of testosterone replacement cannot be recommended.
- Although oral methyltestosterone (a tablet form of testosterone replacement) is still available in North America, it cannot be prescribed in Australia.
- Transdermal testosterone therapy does not adversely affect blood cholesterol levels when administered with oestrogen short term. Long term data is not available. Without oestrogen replacement however, testosterone therapy could potentially negatively affect blood cholesterol levels.
- Cosmetic side effects of testosterone therapy are extremely rare when blood levels are kept in the normal range for women, hence monitoring with blood tests during treatment is essential. Potential masculinising effects include the development of acne, increased body hair, balding and deepening of the voice. Testosterone therapy therefore should not be used by women who suffer from any of these conditions.
- There is little available information regarding the influence of testosterone on breast cancer development. However 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 and two Australian studies have not shown and increased rate of breast cancer in women treated with testosterone.

Conclusion

Androgens are important hormones in women, having diverse biological actions throughout life. The decline in androgen production by both the adrenal glands and the ovaries which begins at least a decade before the average age of naturally occurring menopause, has a significant impact on the physical, psychological and sexual well being of women.

The clinical repercussions of androgen insufficiency in women have only recently been recognised and although still controversial in some countries, testosterone therapy for symptomatic women is becoming an increasingly available option. Unfortunately treatment is limited by the lack of user-friendly testosterone formulations, but the development of various formulations delivering testosterone through the skin may change this.

Side effects of testosterone therapy are a concern for doctors inexperienced in androgen therapy for in women. Genuine side effects are in fact rare when a regimen is instituted by a physician familiar with this form of therapy and women are properly monitored.