

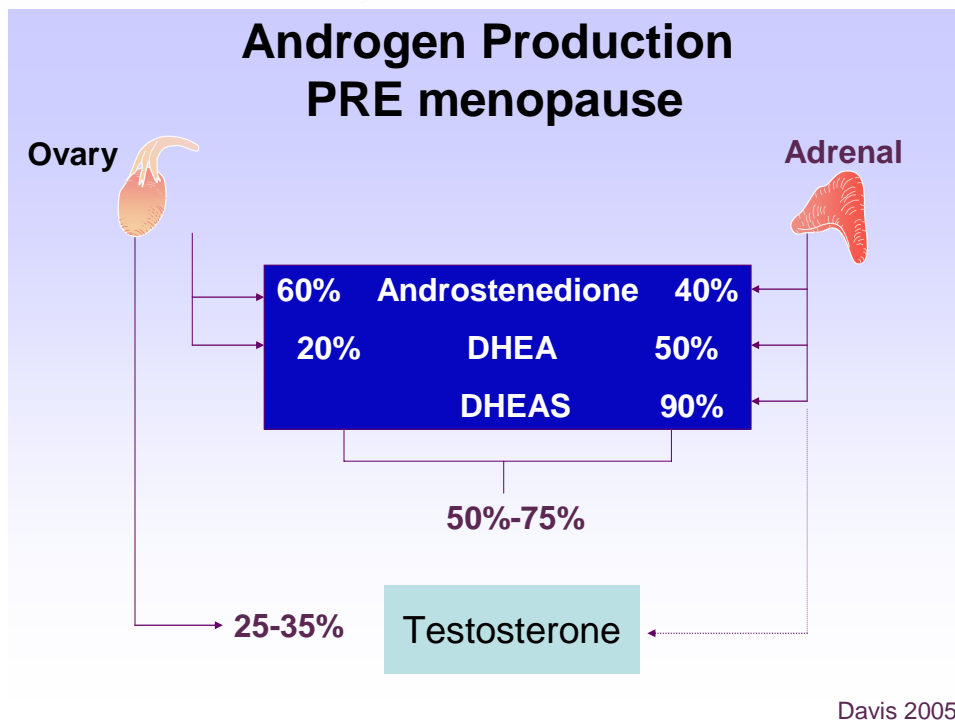
## Androgens in women©

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 sex hormones of major physiological significance in women, being important for maintaining strong muscles and bones, positive protein balance, sexual desire and overall well being. Women who suffer androgen insufficiency experience a variety of physical and psychological symptoms which affect their quality of life. These include fatigue, depression, low libido, muscle weakness and bone loss.

## What are androgens?

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 percent of testosterone is produced by the ovaries and adrenal glands and released directly into the blood stream. The other fifty percent is made from conversion of the adrenal androgens to testosterone in other parts of the body. Adrenal androgens are very important hormones as they are the main source of both testosterone and oestrogen after menopause. In fact, the level of one of the adrenal 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 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.

Very little testosterone circulates freely in the blood stream. Instead ninety-nine percent 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 masculinised 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.



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.

### 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-ageing 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 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 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 replacement, 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 preceding 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 postmenopausal 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 postmenopausal 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 woman has said, results not only in loss of femininity, but of sexual 'personhood'. Such women are usually very responsive to testosterone replacement therapy, and the significance of restoring sexuality to these women must not be overvalued.



## **Androgens and bone**

Androgenic hormones are known to be important in the maintenance of bone mass in both men and women. Even before menopause, bone mass in women is associated with blood testosterone levels with greater bone mass observed in women with higher levels of circulating free testosterone. Androgens stimulate bone cell activity and hence bone formation. In contrast oestrogen inhibits the cells which breakdown bone and thus blocks bone reabsorption. Therefore after menopause, oestrogen replacement therapy prevents loss of bone by blocking the activity of bone reabsorbing cells. There is strong evidence that testosterone replacement after menopause enhances bone formation and in combination with oestrogen actually increases bone mass. At this time, low bone density is not an indication for testosterone treatment, however, testosterone replacement appears to potentially have an important therapeutic role in the prevention and treatment of postmenopausal bone loss which warrants further investigation.



## Androgen therapy

Oestrogen replacement 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 replacement 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 replacement 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 replacement for women is available in the form of testosterone implants and injections. No form of oral testosterone has been designed for or approved for use in women in Australia. 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 – only injections in this context. An injectable form of testosterone combined with oestrogen is available but little used as it must be given frequently and many women find this alternative both uncomfortable and inconvenient.

Testosterone implants at present seem to be the best option for androgen replacement in women. They are approved for this purpose 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 they 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. It has been suggested that these observed effects of testosterone replacement occur because testosterone is converted to oestrogen in the brain and then the increased level of brain oestrogen induces these changes. However, women treated with oestrogen only do not experience the same sexual enhancement as those given combined oestrogen and testosterone therapy.



## Adrenal androgens in women

As outlined earlier, the adrenal glands are vital sources of sex hormones for both men and women. These glands are quiescent during early childhood but switch on, the triggers for this being unknown, and begin to produce sufficient androgens in prepubertal boys and girls to induce the first changes of puberty known as adrenarche. This increase in adrenal hormones, induces sexual hair growth, increased oiliness of the skin and scalp and adult body odour, and paves the way for sexual maturation. Although from the mid thirties on, the adrenal hormone DHEA declines linearly with age in both men and women, it is the main natural sex hormone produced in the body of women after menopause. It is converted in body tissues to both oestrogen and testosterone, although it is unclear as to which of these latter hormones is mostly responsible for the biological effects of DHEA. Its effects are probably mediated through both. DHEA has also been hailed as a possible “antiaging drug”, “reinstating the essence of youth”. Replacement therapy with DHEA to women with advancing age results in restoration of androgen levels, including testosterone and DHEA itself, to premenopausal levels. It has been reported that DHEA therapy results in enhanced well being and increased energy with variable effects on libido described. Preliminary evidence indicates DHEA may protect against bone loss after menopause, or even result in increased bone formation but this requires further evaluation and documentation. Multiple other biological effects have been attributed to DHEA therapy including anticancer actions and immune system stimulation alongside claims that it can be used to treat illnesses such as chronic fatigue syndrome. At this point in time, the therapeutic role of DHEA remains both unclear and controversial. There have been some concerns about toxic effects of DHEA in humans and at this point in time it should not be taken by humans outside the confines of a properly conducted and monitored research study.



### Important points regarding testosterone therapy

- Testosterone therapy should not be given to postmenopausal women without oestrogen replacement simultaneously.
- When administered by testosterone implants or injections, 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 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. Methyltestosterone taken orally can have undesirable effects on the liver and it should not be used.
- Testosterone implants when used for testosterone treatment of women do not adversely affect blood cholesterol levels when administered with oestrogen. 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 no available information regarding the influence of testosterone on breast cancer development. Certainly there is no evidence to date that testosterone treatment via implants affects breast cancer occurrence.
- Testosterone treatment does not make women gain weight. Postmenopausal women treated with oestrogen and testosterone implants usually experience a modest increase in muscle bulk, a reduction in total body fat, but not change in overall body weight.



## 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 replacement 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 a testosterone patch for women is highly likely in the near future.

Side effects of testosterone replacement are a concern for doctors inexperienced in androgen therapy for in women. Genuine side effects are in fact rare when a replacement regimen is instituted by a physician familiar with this form of therapy and women properly monitored. However testosterone implants should only be administered by a physician experienced in the procedure and the effects of this therapy and only with concurrent oestrogen replacement.

The option of testosterone replacement is important for all postmenopausal women but particularly for young women who should be at their prime in terms of sexuality but are robbed of this celebration of life by their experience of either premature or surgically induced menopause.