

Testosterone Replacement for Women



**Southern Ontario
Fertility Technologies**

Introduction

The purpose of this article is to describe the clinical aspects of testosterone replacement for females presenting with decreased libido. Despite a great deal of interest in this form of treatment, relatively little research has been carried out and the use of testosterone replacement for women remains “off label” for many products.

Sexual Function and Dysfunction

Good sex involves many variables. It is determined by each partners’ previous experience, preconceptions, and needs; the relationship and the desire it generates as well as complex other factors including the situation, general health, sex drive and hormonal factors. Although it is not the purpose of this article to discuss sexual dysfunction, some discussion is a pre-requisite for understanding the place of testosterone replacement for women with decreased libido.

For sex to work for both men and women, **four** basic elements need to be present. **(1)Normal hormonal status** is important. Testosterone is the main sexual driver for men but is also important for women. Estrogen is also important for females both for sex drive but also to enable pleasant, non-painful intercourse by preventing atrophic vaginitis.

An **(2) intact vascular and (3) neural supply** to the genital area is important and can be impaired by age and certain medical conditions.

(4)Normal sexually-stimulating thoughts and images must also be present. It is dependant on many factors **including testosterone levels**.

In the normal sexual response, there are five stages for both men and women. They may differ in their timing and importance but help to understand the dysfunctions that can occur for both sexes.

The first stage of a sexual response is **drive and desire**. Drive is the need for, or interest in sexual activity in general. Drive is a basic human need and its level is probably genetically and hormonally determined. It is usually greater in males than females but not always. Desire is person-specific and is sometimes more developed in females but not always. Decreased drive may be more dependant on general health were decreased desire is usually dependant on relationships.

Arousal is the next stage of the sexual response and occurs when more focused sexual thoughts occur. It causes genital vascular engorgement leading to penile erection in males and vulvar and clitoral engorgement and vaginal lubrication in females. Arousal usually increases in a progressive fashion but waxes and wanes in its progress are not uncommon, abnormal or necessarily undesirable.

During the **plateau stage**, the individual remains in a state of high sexual arousal. The duration of this stage is variable between individuals and in the same individual on different occasions depending upon circumstances. Plateau stage may or may not lead to orgasm.

Orgasm involves an acute increase in erotic sensations and involuntary muscle contractions. It produces ejaculation in the male. In the female, orgasm produces involuntary contractions of the vaginal and perineal (around the vaginal opening) muscles. Some women

have glandular tissue related to the prostate tissue in the male than may release a small amount of fluid at the time of orgasm.

Resolution is the final stage of the sexual response when the body returns to its normal resting state. This is a great time for relationship building.

The five stages usually occur in order. They differ in men and women in that the resolution stage usually involves a **refractory period** in men during which it is not possible to experience further arousal. The length of this refractory period varies between individuals and tends to increase with age. Women do not have a refractory period and potentially can experience multiple orgasms.

The classification of sexual disorders reflects the stages of the sexual response and is based on the fourth revision of the **Diagnostic and Statistical Manual of Mental Disorders produced by the American Psychiatric Association**. A formal definition also includes modifiers and general and specific medical conditions, however, the main structure of the classification mirrors the stages of the sexual response and is important to understanding where testosterone replacement is of benefit. Women presenting with “decreased libido” usually have decreased sex drive. Commonly, this spills over to cause decreased arousal and orgasm but **the main indication for testosterone is decreased sex drive**.

It is important to ask about the characteristics of the decreased drive as they determine the treatment required and predict the response to treatment. For example, is it acquired or has it been life long, and is it situational or generalized, and is it gradual in onset or associated with some other life event.

Measurement of Testosterone Level

Controversy exists about the importance of testosterone level. Free testosterone level is much more informative than total testosterone. Low free testosterone does not always correlate with low libido and does not predict a response to testosterone. Some women are more susceptible to low testosterone.

Other Considerations before Testosterone Replacement

A history and directed physical examination are important. Patients with a past or present tendency to **hirsutism** may respond with an exacerbation. This does not represent a contraindication but should be discussed with the patient and testosterone begun at a lower dose. The majority of patients that get hirsutism prefer to continue testosterone and treat the hirsutism.

Patients with a history of **acne** may get acne. This is usually mild and self-limited and tolerated by the patient. Patients with a history of vesicular acne as a teenager may have a severe recurrence.

Testosterone can affect blood sugar, cholesterol, electrolytes and liver or renal function. It is reasonable to screen these parameters especially if other risk factors are present but I have not found any significant changes in them in my practice.

It is important to consider is the **estrogen status** older woman and put these findings in context with the sexual history. If the woman has decreased estrogen and the classical signs of atrophic vaginitis but has remained sexually active to please her husband or because she enjoys the closeness, intercourse may not be painful despite a thin vaginal mucosa. If the couple has continued to have intercourse despite discomfort, there may be redness or micro abrasions present in addition to signs of atrophic vaginitis. Often decreased libido has lead to avoidance of

sexual intercourse but existing atrophic vaginitis will undoubtedly produce symptoms when the couple re-introduces intercourse.

Some men are at high risk for sexual dysfunction once they resume regular sexual intercourse. This cannot always be predicted and may have to be detected on follow-up.

Testosterone Replacement and Libido

In my practice, 78% of women presenting with decreased libido respond to testosterone replacement. Of those that respond only 4% discontinue the treatment because of side effects. There are several predictors of success.

Sexual dysfunction, as outlined above can occur at any stage of the normal sexual response. Women presenting with decreased libido have either decreased sex drive or decreased sexual desire which should be carefully distinguished. I usually ask if the woman responds to sexually stimulating stimuli like erotic or romantic movies. If she does, but no longer responds to sexual partner, the decreased libido may be decreased desire due to a relationship problem or poor sexual technique. This will require relationship or sex counseling. If the decreased libido is a total loss of drive, the response rate to testosterone is greater than 90%.

Complete loss of drive, is usually accompanied by a loss of arousal and decreased orgasm. If these additional complaints are missing, testosterone replacement does not seem to be as effective. Women who do have decreased arousal and orgasm almost always respond to testosterone.

Menopausal status is more predictive of a positive response than age alone. In fact, the strongest predictor of success is the history of a hysterectomy with bilateral salpingoophorectomy (BSO). The only failures in my practice have been when estrogen replacement has been contraindicated. Interestingly, most women who have had this surgery have presented about 18 months after the surgery as the decreased libido seems to be delayed by almost a year.

Women who are perimenopausal and still have some menstruation respond far less frequently to testosterone than those that have had complete cessation of their menstruation. This seems to be the pattern despite other positive predictors of success. In the perimenopausal woman considering testosterone replacement, it is important some method of birth control is in place as testosterone is contraindicated in pregnancy. Menopausal women including those with premature ovarian failure respond very well.

The only exception to menopause as a positive predictor for success is the use of testosterone in younger women on oral contraceptive. Occasionally women will respond to oral contraceptives with a remarkable drop in libido. On rare occasions, where alternate methods of birth control are not acceptable, testosterone replacement is very effective. These women will almost always have extremely low free testosterone levels probably because the oral contraceptive has increased sex hormone binding globulin. Interestingly, I have also tested the free testosterone in a number of women on oral contraceptive who have normal libido and found it similarly decreased. This probably represents individual differences in susceptibility to low testosterone.

Another extremely strong predictor for success is the history of a normal libido and normal sex life in the past. In the few women who describe a lifelong decreased libido, the response to testosterone is very poor but not always absent. Women presenting because they desire treatment respond better than if the consultation has been at the assistance of a partner.

Methods of Replacing Testosterone

There are many ways of replacing testosterone for females. Most commercial testosterone products have been produced for males but with dosage adjustments can be used for females.

Testosterone is available orally as **Andriol**® (testosterone undecanoate, 40 mg per tablet). In my experience, it is not very effective for women and many women who don't respond to Andriol will responded very well to other forms of replacement.

The testosterone patch, **Androderm**® (12.2 or 24.3 mg testosterone per patch) is used for testosterone replacement in males and is not really useful for females. The lowest dose is too high for females and the patch is difficult to cut as it has a central drug delivery reservoir surrounded by a peripheral adhesive area. Once cut, it doesn't stick well.

Androgel® (2.5 and 5.0 gram single dose aluminum packets) has been useful and can be applied as a half a 2.5 gram package (delivering 12.5 mg of testosterone) per day. Accurate dosaging and expense are problems.

Testosterone can also be **formulated in a cream** by a compounding pharmacist, usually 3% or 6% testosterone in vanishing cream. Dosages are usually one to two ml. per day and can be accurately titrated.

Injectable testosterone is my preferred delivery route. It is the most reliable as I have never had a patient who responded to another delivery route not respond to injectable testosterone and I have had many patients who were not responsive to another forms of testosterone who responded to injectable testosterone. Sometimes, if the patient wishes another delivery method, I will establish their response with injectable testosterone and then switch them to another form, usually a compounded cream or androgel. Only about 50% of patients are happy with the switch.

Climacterone® is a depot combination of estrogen and testosterone (testosterone enanthate benzillic acid hydrazone 150 mg, estradiol dienathate 7.5 mg, estradiol benzoate 1 mg per 1 ml.) which was extremely popular with many clinicians and patients. It delivers 69 mg of testosterone and some estrogen in the usual 1 ml. injection. Many gynecologists used it postoperatively for women after a hysterectomy with bilateral salpingoophorectomy. Unfortunately, Climacterone has been recently discontinued. In the past, I have found users of Climacterone very reluctant to switch. Its discontinuation will probably be very unpopular with its users.

Because I prefer to give the estrogen component separately, I usually use **Delatestryl**© (testosterone enanthate 200 mg per ml.). The usual starting dose is 0.5 ml. or 100 mg of testosterone IM once per month. I arrange to see the patients several times to assess their response to treatment and advise dosage adjustments. About 40% of patients remain at this dose and about 20% of patients require a reduced dose and 40% require a higher dose. Dosage ranges from 0.3 ml. (60 mg) per month to 1.6 ml. (320 mg) per month. Side effects seem to be proportional to the dose so the goal is to give the smallest dose that produces the desired improvement in libido. In situations were the required dose causes side effects (usually hirsutism), the patients often choose to continue and treat the undesired effect.

Delatestryl in combination with some form of estrogen will probably be a good replacement for Climacterone users and is fortunately an "on-label" product.

Side Effects

The **short term** side effects of testosterone replacement are usually mild and well tolerated resulting in only a 4% discontinuation rate. Mild **hirsutism** occurs in 20% of women. This can often be minimized by dosage adjustments. Often, the dose can be decreased, hoping to decrease the hirsutism while maintaining the increased libido. This is usually possible but even when mild hirsutism remains many women prefer to wax or bleach rather than give up the beneficial effects on their libido. It is however, the most common reason for discontinuation of the treatment.

Testosterone replacement can also precipitate **acne**. This seems to be more common in women who have a history of moderate acne as a teenager and is especially common in women who continued to have acne past their teenaged years. It is usually confined to a few pustules and limited to the first few months of replacement. Most women tolerate this and it responds to the usual acne treatments. The only patient that discontinued testosterone because of acne had vesicular acne as a teenager and developed an intense acne response to replacement.

Testosterone usually causes increased energy levels but occasionally appears to increase **agitation, insomnia and even aggressive behavior**. This is extremely rare and usually responds to dose adjustments.

Long term side effects have not been documented.

Other Benefits

Over 40% of women experience an **increase in energy level** and 20% of patients will report an **increase in well being**. Many patients report an improvement in their relationship, improved self image, more confidence, and increased exercise tolerance and strength.

One particular benefit in many women is a substantial **decrease in hot flashes** and night sweats. In fact, this finding is so substantial that I frequently use testosterone replacement in women who have disturbing hot flashes despite increases in their estrogen replacement.

Case Studies

#1 – Mrs. A.L.

Mrs. A.L. was a 33 year old woman who presented with decreased libido 2 years after a hysterectomy and bilateral salpingo-oophorectomy (BSO) for severe endometriosis. After the hysterectomy she was given a single injection of Climacterone and then started on conjugated estrogen sulfate (CES) 0.3 mg daily.

She had life-long painful endometriosis with multiple surgical and medical treatments to control her symptoms. She had one child as a result of IVF.

Her sex life has been excellent despite moderate dyspareunia in between various treatments but her interest in sex had decreased drastically over the last 9 months. She and her husband continued to have intercourse because she enjoyed the closeness despite her general lack of interest. However, with the decreased interest she had also experienced a lack of lubrication for which she had started lubricants. She had not had an orgasm for the last 4 months despite the fact that she had consistently reached orgasm earlier in their relationship.

General physical examination was normal with signs of vaginal mucosal thinning on pelvic examination. Free testosterone was below normal and a CBC, blood sugar, cholesterol, electrolytes, renal and liver function tests were normal.

She was started on Delatestryl 0.5 ml (=100 mg) IM monthly. She returned for follow-up and her fourth injection. She was delighted with the return of her interest in sex. Vaginal lubrication had returned and she was able to reach climax consistently. She also noticed an increased energy level and generally felt better about herself and her relationship with her husband. Her husband was also delighted. She was told to continue the present dose and return only if problems developed. She is still continuing the same dose 4.5 years later.

Key Clinical Take-Away Points

- 1) Usually decreased libido presents about 18 months after BSO
- 2) BSO predicts excellent response to treatment
- 3) Decreased libido acquired (not lifelong) predicts better chance of response
- 4) Decreased arousal and orgasm often accompany decreased drive
- 5) Arousal and orgasm often return with return of drive with treatment
- 6) Thin vaginal mucosa may not be symptomatic if the couple has remained sexually active
- 7) Other benefits (increased energy, well-being and improved relationship) may also occur

#2 - Mrs. T.J.

Mrs. T.J. was a 50 year old woman presents with 12 month history of complete loss of interest in sex. Her menopause occurred at 47 years old and she had hot flashes and night sweats were effectively treated with oral estrogen and progesterone. She did very well with almost complete relieved of her menopausal symptoms until recently when there has been a moderate recurrence of them.

She and her husband enjoyed a good sex life together and had three children. As Mrs. T.J.'s interest in sex decreases, the couple's frequency of intercourse decreased. She stopped having orgasms even though she had orgasms 50% of the time as a younger woman. Her husband began experiencing difficulty maintaining an erection and so the couple stopped having intercourse for the last 6 months.

General physical examination was normal and most blood test screening had been done with her yearly physical examination 3 months earlier.

She was started on 1 ml of 6% testosterone in vanishing cream to be applied once per day. She returned after 3 months to report a 30% return of her sexual interest. She also reported some improvement in her hot flashes.

Because of only a modest improvement, she was offered either an increased dose of her testosterone cream or monthly testosterone injections. She requested testosterone injections and was started on Delatestryl 0.5 ml IM monthly. She returned after 3 months to report a 100% return of her sex drive and a 90% improvement in her hot flashes. However, the testosterone had caused some acne which seemed to be getting better now and an increase in upper lip and chin hair. Also, her husband could not ejaculate and would loose his erection after 10 or 15 minutes of intercourse. It was therefore elected to try a decreased dose of 0.3 ml (60 mg.) IM per month and send the couple for sexual counseling. At a review in three months her sex drive was only 50% better and she requested an increase back to the 0.5 ml. dose. Her husband's ejaculation problem had responded to the therapy. She waxes her chin and upper lip and remains on the same dose 2 years later.

Key Clinical Take Home Points

- 1) Female sexual dysfunction often leads to sexual dysfunction in the partner
- 2) Decreased drive may lead to avoidance of sex
- 3) Other delivery systems for testosterone may not be as reliable as IM injection
- 4) History of avoidance of sex or male sexual dysfunction may predict male problems when sex is re-instated
- 5) Sexual counseling may be required with testosterone replacement
- 6) Dose adjustments of testosterone should balance response and side effects
- 7) Mild side effects from the testosterone are often acceptable and treatable

#3 – Mrs. A.S.

Mrs. A.S. was a 44 year old woman with normal menstrual cycles and no health problems who presented because of no sexual interest despite a new romantic relationship. Her menstrual cycles were normal and she had no other health problems. Her current partner had had a vasectomy. A free testosterone had been done by her family doctor and was below normal.

Mrs. A. S. had two previous sexual relationships and stated she had never had much of a sex drive and in fact had never had an orgasm during intercourse. She had presented because her present partner had encouraged (or insisted!) her to seek help. They were very sexually active and she enjoyed the closeness it brought to the relationship.

She was started on Delatestryl 0.5 ml IM monthly and received two injections but failed to attend for her third injection. On a follow-up phone call, she stated she had experienced no improvement in her sex drive and was not interested in trying an increased dose. She was offered sex counseling but refused as she was happy with her current circumstances.

Key Clinical Take Home Points

- 1) Normal menstrual cycles predict a poor response to testosterone
- 2) If testosterone is considered, adequate birth control must be in place
- 3) Low free testosterone is not always predictive of a response to testosterone
- 4) Lifelong decreased libido predicts a poor response to testosterone
- 5) Presentation for consultation initiated by partner predicts poor response
- 6) Many women with low sex drive may be happy with closeness and relationship benefits sex brings despite not decreased drive, arousal and orgasm

#4 – Miss. M. F.

Miss M.F. was a 24 year old woman in a steady sexual relationship. She presented because of decreased interest and response to sex. She and her boyfriend began a sexual relationship two years ago. At first she was not on the oral contraceptive (OCP) but did start after 3 months (Marvelon ®). She was delighted with the way the OCP decreased the heaviness and painfulness of her periods but over the first year of taking the pill she noticed a complete loss of her sexual interest. She continued to have sex to please her boyfriend but had trouble with vaginal dryness and could not reach orgasm.

Blood tests demonstrated a normal total testosterone but an extremely low free testosterone. It was therefore decided to discontinue the oral contraceptive and try Depo-Provera ®. Unfortunately, she experienced almost continual spotting and gained 35 pounds. The Depo-

Provera was stopped and an IUD (Nova T ®) used. This caused very heavy and painful periods and had to be removed.

With most other effective birth control methods exhausted, it was elected to restart the Marvelon and try Delatestryl 0.5 mg IM monthly. A review after three months demonstrated her periods had become better again and her sex drive was restored. It was suggested she continue but she was counseled that she must discontinue the Delatestryl when she discontinues the OCP.

Key Clinical Take Home Points

- 1) Oral contraceptive may decrease free testosterone by increasing sex-hormone binding globulin
- 2) Oral contraceptive, in susceptible women, may decrease sex drive
- 3) If no other alternatives, testosterone may re-instate sex drive
- 4) This is a very controversial use of testosterone replacement
- 5) Testosterone is contraindicated in pregnancy as it may masculinize a female fetus

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Southern Ontario Fertility Technologies (S.O.F.T.)
555 Southdale Rd.E., Suite 107,
London, Ontario, N6E1A2.
Tel 519 685-5559