



Testosterone Is a Contraceptive and Should Not Be Used in Men Who Desire Fertility

Amir Shahreza Patel¹, Joon Yau Leong², Libert Ramos¹, Ranjith Ramasamy¹

¹Department of Urology, University of Miami Miller School of Medicine, Miami, FL, ²Department of Urology, Thomas Jefferson University, Philadelphia, PA, USA

Testosterone has a variety of functions and is commonly used in older men to treat symptoms of hypogonadism, such as decreased libido, decreased mood and erectile dysfunction. Despite its positive effects on sexual function, it has a negative effect on fertility. Exogenous testosterone therapy can negatively affect the hypothalamic-pituitary gonadal axis and inhibit the production of follicle stimulating hormone and luteinizing hormone. The purpose of this review is to discuss the contraceptive properties of testosterone therapy and to discuss strategies to increase testosterone in men with the desire to preserve fertility.

Keywords: Contraception; Family planning services; Hypogonadism; Infertility; Testosterone; Testosterone replacement therapy

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INTRODUCTION

Testosterone is a pleiotropic hormone that plays various physiological roles in the development of male genitalia in utero and during puberty. Classically, testosterone is a hormone associated with masculinity. Testosterone is used as treatment for males with late onset hypogonadism, a condition in men who experience symptoms caused by a decrease in serum testosterone. Symptoms associated with low testosterone can include decreased libido, decreased muscle mass, depressed mood and/or erectile dysfunction. The use of testosterone replacement therapy (TRT) among men over the age of 40 years has increased more than 3-fold over the last decade [1].

Exogenous testosterone comes in various preparations and each form carries various risks. Along with an increase in hematocrit, a major adverse effect of TRT is the diminished sperm production because of the decreased intra-testicular concentration of testosterone and suppression of the hypothalamic-pituitary-gonadal (HPG) axis [2-4]. Suppression of follicle stimulating hormone (FSH) release from the pituitary gland impairs sperm production and suppression of luteinizing hormone (LH) release inhibits intra-testicular testosterone production.

The purpose of this review is to evaluate the contraceptive effect of testosterone, discuss how the use of exogenous testosterone can negatively impact a man's fecundity and identify the importance of family plan-

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Correspondence to: Amir Shahreza Patel <https://orcid.org/0000-0002-6298-6421>

Department of Urology, University of Miami Miller School of Medicine, 1120 NW 14th Street, Suite 1551, Miami, FL 33136, USA.

Tel: +1-305-497-7813, **Fax:** +1-305-243-6597, **E-mail:** asp136@med.miami.edu

ning in men who are planning to receive TRT.

PHYSIOLOGY OF TESTOSTERONE

In healthy adult men, testosterone production is precisely regulated by the HPG axis. Higher cortical centers in the brain signal the hypothalamus to secrete gonadotropin-releasing hormone (GnRH) in a pulsatile fashion. GnRH in turn stimulates the release of LH and FSH from the anterior pituitary which modulates testosterone production from the Leydig cells and spermatogenesis by the Sertoli cells, respectively. As testosterone levels increase, negative feedback suppression is exerted on the androgen receptors in the hypothalamic neurons and pituitary gland, thereby inhibiting the release of GnRH, FSH and LH [5].

The Endocrine Society and American Urological Association (AUA) recommends treating symptomatic men with low testosterone documented on two morning fasting serum total testosterone concentrations. Both organizations recommend against the use of testosterone for treatment of hypogonadism in men who desire fertility in the next 6 to 12 months [3,4].

The exogenous administration of testosterone suppresses the release of gonadotropins (FSH and LH) to levels below that required for spermatogenesis. Spermatogenesis is largely dependent on the action of FSH on Sertoli cells coupled with high intra-testicular testosterone concentrations. Within the seminiferous tubules, only Sertoli cells possess receptors for both FSH and testosterone. Numerous signaling pathways are activated when FSH binds to FSH receptors on these cells. It acts synergistically with testosterone to increase fertility and the efficiency of spermatogenesis [6]. The inhibition of LH release by exogenous testosterone leads to the suppression of endogenous testosterone production by the Leydig cells. The decreased intra-testicular testosterone combined with the suppression of FSH leads to decreased germ cell survival and maturation (Fig. 1).

Intra-testicular testosterone is required in spermatogenesis for the formation of the blood-testis barrier (BTB). The BTB is a series of tight and adherens junctions between the Sertoli cells that separates post-meiotic germ cells in the adluminal compartment of the seminiferous tubules from the basal compartment containing the blood supply. During spermatogenesis, the BTB is disrupted and reformed as preleptotene

spermatocytes pass through this barrier. In the absence of testosterone stimulation, spermatogenesis can only proceed as far as the prophase 1-leptotene stage of meiosis [7].

Testosterone is also required in maintaining connections between Sertoli cells and the haploid spermatid germ cells. Round spermatids are initially connected to Sertoli cells via desmosomes. As the spermatids mature and elongate, the desmosomes are replaced with stronger, specialized adherens junctions called ectoplasmic specializations, which are maintained until the release of mature sperm. Testosterone aids in this process and increases the efficiency of germ cell attachment to Sertoli cells. Testosterone is also essential for the release of mature spermatozoa from Sertoli cells. It has been shown that in the absence of testosterone stimulation, sperm are not released but are instead phagocytized by Sertoli cells [7].

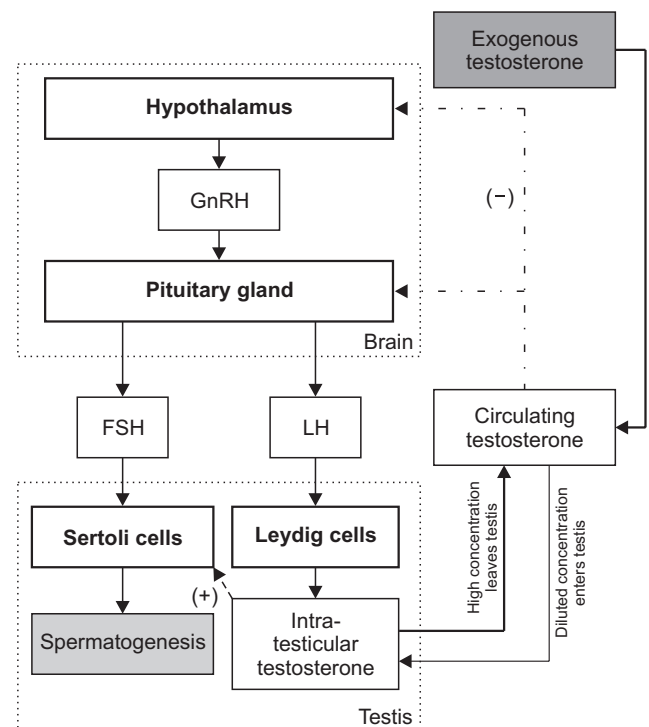


Fig. 1. Image explaining the contraceptive effect of exogenous testosterone. In summary, it works by 2 mechanisms, decreasing intra-testicular testosterone, and inhibiting spermatogenesis. Most of the intra-testicular testosterone is made by the Leydig Cells in the testis. When exogenous testosterone is present, it inhibits gonadotropin-releasing hormone (GnRH) production which in turn inhibits luteinizing hormone (LH) production and decreases endogenous testosterone production by the Leydig cells, decreasing the intra-testicular testosterone concentration. Inhibiting GnRH production also inhibits follicle stimulating hormone (FSH) release, which impairs spermatogenesis in the Sertoli cells.

Ultimately, the low intra-testicular testosterone results in decreased proliferation of spermatogonia, defects in spermiation of mature spermatozoa by Sertoli cells and accelerated apoptosis of spermatozoa [8-11]. Since 80% of testicular volume consists of germinal epithelium and seminiferous tubules, a reduction in these cells is usually manifested by testicular atrophy and this reflects the loss of both spermatogenesis and Leydig cell function [12,13].

Testosterone as a contraceptive can suppress spermatogenesis and lead to azoospermia in 65% of normospermic men within 4 months of use [14]. Cessation of exogenous testosterone will lead to the reversal of hormonally-induced azoospermia in 64% to 84% of men with a median time of about 110 days [13-15]. All men in these studies recovered to baseline levels after cessation of therapy; however, it took up to 2 years for some men to recover. These studies were performed in a controlled setting for a clinical trial, with a limited duration of testosterone use. In actual practice, recovery may not be as pronounced. Kohn et al [16] studied spermatogenesis recovery with human chorionic gonadotropin (hCG) and selective estrogen receptor modulators (SERM) in men with infertility associated with testosterone use. Thirty percent of the 66 men were not able to achieve a total motile sperm count of more than 5 million after 12 months in the study. They found that the failure of recovery is associated with older patients and longer TRT duration.

If fertility is affected because of TRT, couples may require the use of *in vitro* fertilization or intra-cytoplasmic sperm injection for future conception. These assistive reproductive technologies are expensive and are not always successful [17,18].

In summary, despite the androgenic effects of testosterone on sexual function, libido and mood; its effect on gonadotropins leads to the inhibition of sperm production [13]. This effect may diminish with the cessation of testosterone intake, but the extent of recovery is not clear for chronic users [16,19].

TESTOSTERONE AS A MALE CONTRACEPTIVE

Compared to the long list of contraceptive options available to women, men are limited to vasectomy and condoms. The former is challenging to reverse and the latter has failure rates as high as 18% because of non-

compliance. Partners who correctly and consistently use condoms have failure rates of 2% [20,21]. As it is a user-dependent method, many couples seek easier to use options like female oral contraceptive pills or intra-uterine devices [22]. However, there is a demand for alternatives. A survey of over 9,000 men from different populations in 2005 found that 29% to 71% of men are interested in using a form of hormonal male contraception [22,23].

In 1978, a newly available oral testosterone preparation known as testosterone undecanoate (TU) was investigated as a possible form for male contraception. The study found that regular testosterone use for 10 to 12 weeks causes suppression of sperm production, and even azoospermia, albeit inconsistently [24]. Ever since that study, testosterone has undergone extensive clinical trials as a hormonal method of male contraception and many have found testosterone to be efficacious, reversible and safe with minimal short-term side effects [23].

Unfortunately, the contraceptive effect of testosterone is not reliable. This has been proven in multiple studies, including two by the World Health Organization (WHO) Task Force on Methods for the Regulation of Male Fertility [14,15,25]. These two studies found an azoospermia rate of 64% to 75% in 6 months with testosterone enanthate [6,7]. A sperm concentration of 3 million/mL was used as a threshold for effective suppression of spermatogenesis in this study [14,15]. In a Chinese study of a monthly intramuscular TU injection, an azoospermia rate of 93% to 98% was achieved after 6 months with 1 million/mL as the criteria for effective suppression [25,26]. The different rates of azoospermia can be explained by the variable criteria and by ethnic differences in testosterone response [26,27]. These studies confirm the effectiveness of testosterone as a contraceptive, and provides evidence that men who desire fertility should not be prescribed TRT.

Even with this evidence, testosterone has not been approved by the USA Food and Drug Administration (FDA) for use as a contraceptive. In 2011, a phase II study for a combined TU/norethisterone enanthate formulation ended prematurely because of higher than anticipated adverse effects including mood changes (such as depression), increased libido, acne and weight gain [27,28].

More recent advancements were shown in the 2018 Endocrine Society meeting, with dimethandrolone un-

decanoate shown to effectively decrease sperm counts without adverse effects in a double-blind study in 2 academic sites. More extensive research on the safety of testosterone as a contraceptive needs to be done before testosterone can be used as a safe and reliable contraceptive [29].

FORMULATIONS OF TESTOSTERONE REPLACEMENT THERAPY

To date, many different testosterone formulations are available, each with their own side effect profiles. The selection of the preparation of testosterone requires a comprehensive discussion with the patient about the route of administration, cost and side effects of the individual formulations.

Oral methyltestosterone is the only form of oral testosterone approved for use in the USA. It is strongly associated with hepatotoxicity and the AUA recommends against using the formulation [2,3]. TU is approved for use in some countries but is not approved for use in the USA [4].

Topical options of TRT include gels and patches. They are relatively easy to administer and doses are able to be quickly altered when needed [30]. Their adverse effects include skin irritation seen with testosterone patches. Topical testosterone gels also run the risk of transference to others; but this can be avoided by using a clothing barrier [31,32].

Nasal testosterone gels (NTG) are a relatively newer form of TRT that is currently undergoing extensive research. It is seen to be advantageous over topical gels because of ease of use and the decreased risk of transference [33]. With regards to fertility, Connors et al [34] found that 4.5% NTG two or three times a day restored serum testosterone levels while only decreasing gonadotropin levels minimally, keeping serum FSH and LH values within the normal range. Its short half-life results in a return of serum testosterone to near baseline levels between doses. It is theorized that this decreases its effect on the pulsatile release of GnRH by the hypothalamus [35]. A phase IV clinical trial is currently evaluating its impact on semen analysis parameters, and it would be the first study to do so [36]. Based on what is found by future studies, NTGs may have the potential to be a suitable TRT option in men desiring fertility.

Intramuscular testosterone injections are another

form of TRT. These include testosterone cypionate and enanthate, which are self-administered once every 1 to 2 weeks. Their starting dose is 100 mg weekly or 200 mg every two weeks before titrating in response to lab results on follow-up visits [3]. While the patients using these formulations will be able to avoid frequent trips to the clinic once the dose has been adjusted, it does require proper patient education to ensure compliance to the dose set by the healthcare provider. They also have a greater risk of side effects than other preparations [30,37]. One of these adverse effects is the 'up and down' phenomenon due to the variable release of the hormone into the bloodstream leading to peaks and troughs beyond the normal range of serum testosterone levels [5,30,38,39].

TU is another preparation of intramuscular testosterone that is longer acting than the other formulations. It needs to be administered with an initial dose of 750 mg, followed 4 weeks later by another 750 mg dose. This is then followed by an intramuscular injection once every 10 weeks. A disadvantage is that this preparation needs to be administered in the office as a slow injection over 2 minutes and patients need to be monitored for 30 to 45 minutes after administration due to the risk of developing pulmonary-oil micro embolism [4,40].

Beyond gels, patches and injections, another option for TRT are the subdermal implants. They are administered in a 10- to 15-minute procedure in the office every three to six months depending on follow-up laboratory results. This is a popular option among patients because they do not have to self-inject or apply gels repeatedly [30]. It is particularly helpful in patients who travel regularly, and the extended release decreases the 'up and down' feelings often experienced with the intramuscular injections. The disadvantages of subdermal implants include the need for regular office visits, pain and bruising at the site of insertion, as well as the minimal risk of infection and pellet extrusion [30].

In terms of the contraceptive effect of the different formulations of testosterone, most research has shown that transdermal and intramuscular testosterone seem to be the strongest contraceptive formulations. The WHO and Chinese studies used testosterone enanthate and TU, respectively. The topical formulations of testosterone have variable contraceptive effects. The testosterone patch was shown to be an ineffective contraceptive [41] while the gel had mixed results [42,43].

However, the sample size for most of these studies are not large enough to truly assess the extent to which fecundity is affected. More research needs to be done to evaluate the contraceptive effect of the various formulations of testosterone.

A list of the available testosterone formulations with its side effect profiles and effect on fertility can be

found in Table 1 [3,14,15,25,28,41-48].

Table 1. List of testosterone formulations

Testosterone formulations (brand)	Dosage and frequency	Adverse effects	Contraceptive effect
Injectable		Inflammation and pain at injection site	
TE (Delatestryl)	50 to 200 mg every one to two weeks	Serum levels tend to have peaks and troughs	A large multicenter trial of weekly TE alone is effective in causing reversible azoospermia and severe oligospermia without major side effects [14,15]. Its contraceptive effect is more effective when combined with 500 mg oral levonorgestrel [44].
Testosterone cypionate (Depo-Testosterone)	50 to 200 mg every one to two weeks	Avoid in soy hypersensitivity	
Testosterone undecanoate (Aveed)	750-mg initial dose and another 750 mg four weeks later, then 750 mg every 10 weeks	Risk of anaphylaxis and pulmonary oil microembolism	A Chinese study of monthly TU is effective in causing reversible azoospermia and severe oligospermia without major side effects [25]. WHO/CONRAD trial testing TU/NETE (norethisterone enanthate) was prematurely terminated due to adverse effects [28].
Topical		Risk of transfer to others, may cause application site irritation	Combined formulation with non-adrenergic progestin gel (Nestorone) effective in causing reversible severe oligospermia and azoospermia with minimal side effects [42].
Transdermal gel			A small study of 18 men found no change in semen parameters when using Androgel alone for the treatment of hypogonadism [43].
Androgel 1%	50 to 100 mg daily		
Androgel 1.62%	20.25 to 81 mg daily		
Fortesta 2%	10 to 70 mg daily		
Testim 1%	50 to 100 mg daily		
Vogelxo 1%	50 to 100 mg daily		
Transdermal patch (Androderm)	2 to 6 mg daily	Skin rash common; patients are advised to rotate application sites	Not effective for use in contraception [41].
Transdermal solution (Axiron)	30 to 120 mg daily	Applied to axillary region; risk of transfer to others, may cause application site irritation, nasopharyngitis	
Buccal testosterone (Striant)	30 mg twice daily	May alter taste or irritate gums and oral mucosa	
Intranasal gel (Natesto)	33 mg; one actuation (11 mg) in each nostril three times daily	Adverse effects include nasal irritation and upper respiratory symptoms	
Subdermal pellets (Testopel)	450 to 900 mg every three to four months	May cause fibrosis, bleeding, infection, pellet extrusion	Combined formulation with etonogestrel implants or oral desogestrel lead to reversible azoospermia in most men [45,46]. Study shows decline in semen parameters after using 800 mg testosterone implants [47]. Contraceptive effect not affected by finasteride [48].

Dosages are based on the 2018 American Urological Association Guidelines [3].

TE: testosterone enanthate, TU: testosterone undecanoate, WHO: World Health Organization.

USING TESTOSTERONE IN THE TREATMENT OF HYPOGONADISM IN MEN WHO DESIRE FERTILITY

Considering that there is abundant evidence demonstrating that TRT significantly decreases sperm production, it is important that clinicians consider the evidenced risks of male infertility before starting patients on TRT. It can be surprising to patients that testosterone can suppress fertility, in contrary to its stimulatory effects on libido and erectile function. The patient's desire for fertility must be discussed in depth and established prior to initiating testosterone. The discussion must also include future thoughts on fertility. This will allow the physician to manage the timing of hypogonadism treatment, essentially balancing the alleviation of hypogonadal symptoms with the patient's desires for fertility. This could also open discussion about cryopreservation of sperm as an option for the patient to preserve fertility further down the line.

Physicians should also educate men already on TRT. There has been an increase in TRT use among men aged 18 to 45 years and more than 20% of these men did not get a baseline testosterone level prior to initiation of TRT [49]. Some of these men may not know about its effects on fertility and may not have discussed it with their prescribing physician. The study also showed that less than 2% of men on TRT obtained a baseline semen analysis [49]. In addition to the routine serum total testosterone, LH, and hematocrit prior to starting TRT, every man of reproductive age should have a baseline semen analysis [3]. The baseline semen analysis will identify men with a decreased baseline sperm count, as a reference value for future semen analyses after TRT use.

If a patient currently desires fertility, TRT should be avoided or discontinued immediately. A semen analysis should be performed if the patient has discontinued TRT. Azoospermia or severe oligospermia may be seen in these patients, but most men should return to baseline semen analyses in 6 to 9 months after cessation of TRT [13-15]. A 2006 integrated analysis showed that 90% of patients were expected to return to baseline sperm concentration values 12 months after cessation of treatment and 100% after 24 months [50]. Furthermore, evidence in a 2015 study of 49 men showed that 3,000 units of hCG subcutaneously every other day is effective in supporting the recovery of spermatogenesis

without significant adverse effects [11].

Regardless, the recovery of spermatogenesis is unclear for patients on chronic TRT. Physicians should take caution when treating hypogonadism in men who desire future fertility, but also acknowledge the reversible azoospermia seen in controlled studies [51]. Adjunctive hCG and clomiphene can be used with TRT to maintain testicular size and intra-testicular testosterone concentrations [52]. Referral to a reproductive urologist should be considered in a male with low testosterone interested in fertility.

ALTERNATIVES TO TESTOSTERONE THERAPY IN PATIENTS WHO WISH TO PRESERVE FERTILITY

Clomiphene and enclomiphene citrate provide an alternative treatment option for hypogonadal men that desire fertility as it does not affect sperm production. Clomiphene is a non-steroidal SERM. It selectively binds to estrogen receptors in the hypothalamus, antagonistically inhibiting negative feedback, increasing the levels of gonadotropins and stimulating the testicular production of testosterone in men [53].

Even though enclomiphene citrate is not currently FDA approved, it has been shown to increase serum testosterone by raising the serum LH and FSH levels without negatively affecting semen parameters [54]. Kaminetsky et al [55] conducted a proof-of-principle, randomized, open-label, fixed dose, controlled, two-center phase IIB study that compared 25 mg of enclomiphene citrate daily to topical testosterone in hypogonadal men. The results showed higher testosterone levels and sperm counts in men receiving enclomiphene citrate. This corroborates with other studies which show improved semen parameters with the use of clomiphene citrate, with some studies describing it as a treatment for male infertility [56,57].

hCG has also been used (often with clomiphene citrate, tamoxifen or anastrozole) because it stimulates the production of endogenous testosterone without compromising spermatogenesis. Although the exact mechanism of action and production site in males are not fully understood, it is known that hCG mimics the effects of LH and stimulates the Leydig cells in the testicles to produce endogenous testosterone [3,58-60]. Additionally, studies have shown that low-dose hCG can be used with TRT to maintain high levels of intra-

testicular testosterone while men are being treated for hypogonadism [52,61]. While hCG is effective in increasing testosterone, various studies have shown that it is also efficacious in inducing spermatogenesis [62,63]. It is even effective in helping with the recovery of spermatogenesis in men who were on TRT [11]. Clinicians generally agree on using 2,000 IU of hCG administered subcutaneously 3 times per week as defined by the 2002 American Association of Clinical Endocrinologists guidelines [64].

The ideal treatment for hypogonadism should provide physiological testosterone levels, exhibit appropriate circadian rhythms and be modulated by the HPG axis. No formulation of testosterone has been able to achieve this. However, there has been recent ongoing research on autograft Leydig stem cells. This may prove to be an effective treatment for hypogonadism in the future as it has the potential to fulfill all the criteria of an ideal TRT [65]. Makala et al [66] found that serum testosterone levels and Leydig cell populations were restored over time in mice who underwent ectopic autografting of testicular tissue. These results indicate that Leydig cells are able to regenerate de novo in the autografted adult testes, subsequently restoring serum testosterone level. In 2017, Zang et al [65] also demonstrated how direct transplantation of stem Leydig cells are capable of self-renewal, extensive proliferation and differentiation into mature Leydig cells. These Leydig cells can then be regulated by the HPG axis and restore the neuroendocrine regulation of testicular function and its diurnal testosterone production system. Having said that, these strategies still face major hurdles with regards to its clinical translatability and the ethics of cell transplantation.

CONCLUSIONS

Testosterone therapy is a contraceptive, albeit a poor one. Men of reproductive age with low testosterone should be counseled on the adverse effects of TRT on fertility. Obtaining a semen analysis and possible cryopreservation of sperm should be offered if TRT is prescribed to men interested in preserving fertility. Options such as clomiphene citrate and hCG along with a referral to a reproductive urologist should be considered to naturally increase testosterone levels in those men with low testosterone who want to avoid TRT.

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Author Contribution

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