

## Exogenous Testosterone as a Risk Factor for Male Infertility and Recommendations for Recovery

Rashad Roberson<sup>1</sup>, Nicholas A Kerna<sup>2\*</sup> and Raymond Nomel<sup>3</sup>

<sup>1</sup>Georgetown American University, College of Medicine, Guyana

<sup>2</sup>SMC–Medical Research, Thailand

<sup>3</sup>All Saints University, College of Medicine, St. Vincent and the Grenadines

**\*Corresponding Author:** Nicholas A Kerna, (mailing address) POB47 Phatphong, Suriwongse Road, Bangkok, Thailand 10500.

Contact: medpublab+drkerna@gmail.com.

**Received:** October 08, 2020; **Published:** November 25, 2020

**DOI:** 10.31080/ecemr.2020.05.00233

### Abstract

Exogenous testosterone use is widespread in the adult male population—with or without age-related infertility or medical necessity. Exogenous testosterone compounds are readily available to the consumer. There are benefits to its indicated and supervised application; however, caution regarding its use is advised. Exogenous testosterone supplementation alters testicular biochemistry, leading to azoospermia and infertility in men, previously unaffected by age-related infertility. Also, long-term use has public health consequences in that it can increase the incidence and prevalence of prostate cancer in otherwise healthy men. Fortunately, in most men unaffected by age-related infertility, there is a return of normal spermatogenesis within one year of discontinuation of exogenous testosterone. This paper reviews and summarizes exogenous testosterone's adverse effects on the male hypothalamic-pituitary-gonad axis, the remedy and recovery thereof, and the public health risk.

**Keywords:** Azoospermia; Exogenous Testosterone, Male Infertility; Spermatogenesis

### Abbreviations

DHT: Dihydrotestosterone; HPG: Hypothalamic-Pituitary-Gonadal; FSH: Follicle-Stimulating Hormone; GnRH: Gonadotropin-Releasing Hormone; hCG: Human Chorionic Gonadotropin; LH: Luteinizing Hormone; OTC: Over-the-Counter; TSH: Thyroid-Stimulating Hormone

### Introduction

Testosterone hormonal supplements and other supplemental androgens are used primarily to treat hypogonadal dysfunction, erectile disorders, and male hormonal contraception [1]. However, many men, who do not have hypogonadal issues, ingest high doses of over-the-counter (OTC) testosterone supplements to boost sexual performance. Other men, especially athletes, use anabolic steroids to increase metabolism, build muscle, enhance endurance performance, and stay in shape. Some members of the aging male population take such supplements to increase energy level for daily personal and work activities.

However, there are adverse effects of testosterone supplementation when taken long-term. Patients who take prescribed or OTC testosterone supplements are equally at risk of shutting down the body's natural testosterone production. Men in their reproductive ages, who take exogenous testosterone for various reasons, including but not limited to hypogonadism, can experience spermatogenesis inhibition [2].

Inappropriate, unregulated, and unsupervised use of exogenous testosterone continues to increase yearly with no decrease (only increase) on the horizon [3]. With no education to the contrary and easy access to testosterone products, consumer-targeted advertising is a contributory factor in this “exogenous-testosterone epidemic”.

### Discussion

#### Review of the hormonal pathway of spermatogenesis

In males, the hypothalamic-pituitary-gonadal (HPG) axis is regulated by the hypothalamus, pituitary, and testes. Many men’s exogenous testosterone supplementation for hormonal contraception, muscle building, or boosting testosterone levels has significant regulatory effects on the HPG axis and spermatogenesis [4,5]. Exogenous testosterone reduces intra-testicular testosterone, diminishing the testes’ functional capacity in the size and production of sperm by altering the process of spermatogenesis. Exogenous testosterone inhibits or halts the endogenous production of testosterone, resulting in azoospermia [6].

The hypothalamus acts as the control center of the reproductive hormonal-axis via negative-feedback. The pituitary also works via negative-feedback, regarding hormones produced and released by the testes. The hypothalamus produces gonadotropin-releasing hormone (GnRH). GnRH reaches the adenohypophysis of the pituitary gland via the venous system. It then triggers the synthesis and release of gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary [7]. LH and FSH are glycopeptides produced in males and females. LH and FSH share an alpha peptide chain with thyroid-stimulating hormone (TSH) and human chorionic gonadotropin (hCG). However, they differ from each other by the presence of a specific beta chain. The beta chain provides a specific pathophysiological function, such as male testicular reproductive function [8].

LH stimulates testosterone secretion in the testis by binding to interstitial cells (Leydig cells), while FSH initiates and sustains the process of spermatogenesis by stimulating sustentacular cells (Sertoli cells) [9,10]. The Sertoli cells line the seminiferous tubules, providing nutrients to sperm. The testicular androgen, testosterone, is transformed into the active form, dihydrotestosterone (DHT) courtesy of 5-alpha-reductase [11], which is responsible for male secondary sexual characteristics and external genitalia, scrotum, penis, and prostate [12]. In this process, the testis produces inhibin (by Sertoli cells), inhibiting the anterior pituitary production of FSH (via negative-feedback); increased blood levels of testosterone inhibit the hypothalamic production of GnRH, causing a decrease in both gonadotropins released from the anterior pituitary [7–10].

The HPG axis begins its normal regulatory process once the exogenous testosterone is no longer available. GnRH in a pulsatile pattern stimulates the release of LH and FSH [13]. Thus, in long-term use, exogenous testosterone inhibits LH and FSH by interrupting the negative-feedback loop, adversely affecting the HPG axis. This interruption leads to the suppression of the concentration of intra-testicular testosterone needed for spermatogenesis’s natural process to occur [3].

In younger males, long-term risks include is gonadal atrophy and premature closure of the epiphyseal plate due to non-pulsatile exogenous testosterone’s inhibitory effect on HPG axis activity [13–15]. For the body to maintain its hormonal homeostasis, the HPG axis processes activate the hypothalamus to stimulate the pulsatile production of GnRH, stimulating LH and FSH [7–10]. Prescribers and consumers of exogenous testosterone cannot overlook this unintentional and undesirable consequence in long-term use.

#### Public health risk

A public health hazard is emerging as more men readily resort to exogenous testosterone, primarily for self-gratification (non-medical necessity). The inappropriate use of exogenous testosterone in men is increasing. Consumer-targeted advertising and easy access to testosterone products contribute to the exogenous testosterone epidemic [3]. Testosterone and other androgenic supplements are available OTC and easily accessible by the general public. Lack of education and health awareness regarding the side effects of the long-term use

of OTC testosterone supplements, testosterone-stimulating substances, and other androgen supplements pose a significant public health risk, particularly in a large population of men developing prostate cancer [16,17].

Men who take these supplements for contraception, muscle building, and various other reasons may not disclose such to their health-care providers to closely monitor their hormonal levels. Consumer advertisements and the media make these products appealing to men urgently seeking a “quick fix” for their sexual performance and physical appearance. This often targeted group of men fall prey to using these testosterone and other androgenic supplements without any medical advice, management, or oversight from a qualified healthcare professional. Patients who take prescribed testosterone or OTC testosterone supplements are equally at risk for the shutting-down or down-regulation of the body’s natural process of testosterone production [4–7].

Androgen use is increasing in men of all age groups. According to Baillargeon, *et al.* (2013): “In the United States, as of 2010, the South has the highest prevalence of androgen use, followed by the West, Midwest, and Northeast. Only about 74.72% of men on androgen therapy from the years 2001–2011 had their testosterone level measured in the preceding 12 months” [18], leaving more than 25% of androgen-using men without baseline testosterone analysis. Table 1 below, developed by Baillargeon, *et al.* (2013), depicts the trend in the prescription of androgens in the United States from 2001 to 2011.

Age Range, y	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
<b>40 - 49</b>											
% Given ART	0.54	0.66	0.76	0.75	0.81	0.90	1.05	1.22	1.66	1.99	2.29
Eligible men, No.	624 080	670 126	703 738	698 074	724 518	715 546	720 046	761 088	729 965	698 380	698 343
<b>50 - 59</b>											
% Given ART	1.02	1.19	1.39	1.36	1.37	1.52	1.69	1.88	2.54	2.98	3.26
Eligible men, No.	424 534	457 417	490 381	501 335	562 482	578 941	605 057	675 508	639 073	625 709	643 106
<b>60 - 69</b>											
% Given ART	1.32	1.53	1.72	1.68	1.69	1.87	2.06	2.28	3.03	3.51	3.75
Eligible men, No.	161 273	182 399	197 578	204 055	234 902	250 808	280 662	331 150	309 766	300 312	317 143
<b>≥ 70</b>											
% Given ART	0.77	0.79	0.99	0.99	1.00	1.13	1.20	0.96	1.92	2.10	2.22
Eligible men, No.	60 925	69 210	71 445	73 181	93 855	95 678	104 750	113 813	103 342	82 203	84 875
<b>All ages</b>											
% Given ART	0.81	0.96	1.11	1.10	1.14	1.20	1.45	1.66	2.23	2.63	2.91
Eligible men, No.	1 270 812	1 379 062	1 463 142	1 476 645	1 615 757	1 640 973	1 710 515	1 881 559	1 782 146	1 706 604	1 743 467

**Table 1:** Percentage of men given androgen replacement therapy by age-group and year.

*Adapted from Baillargeon, et al. (2013) [18].*

**Mechanism of adverse effects**

Exogenous testosterone has an inhibitory effect on the HPG axis. It reduces intratesticular testosterone and, thus, decreases the functional capacity of the testis in size and production of sperm, leading to azoospermia [4–6,9,10]. Clinicians might overlook that a male

patient, with no history of a hypogonadal issue, could be using exogenous testosterone, a risk for undesirable sequelae affecting the HPG axis, leading to the suppression of intratesticular testosterone concentration. Potentially, as spermatogenesis becomes inhibited, azoospermia and male infertility can occur—leading to male infertility [4–6,9,10].

### Recovery from the adverse effects of long-term exogenous testosterone use

The positive news is that the discontinuation of exogenous testosterone can result in recovery and a return to normal levels of intratesticular testosterone concentration, as demonstrated in a study by Liu, *et al.* (2006) [19]. In this study, the researchers performed an integrated, multivariate, time-to-event analysis of available data from individual participants in thirty studies, published from 1990 to 2005.

Sperm output was monitored monthly after post-hormonal treatments, including testosterone supplements. The research's primary aim was to determine the recovery time of sperm concentration to a threshold of 20 million per mL (as an indicator of fertility). The statistical analysis involved univariate and multivariate analysis, using Kaplan-Meier and Cox's methods.

The results were more in favor of the older men, Asian origin, shorter treatment duration, shorter-acting exogenous testosterone, and those with baseline higher sperm concentration and lower blood concentration of LH. The study results were encouraging, pointing to the restoration of intra-testicular testosterone to about 20 million per mL by 67% of participants within 6 months, to about 90% within 12 months, to about 96% within 16 months, and to nearly 100 % within 24 months of the discontinuation of hormonal/testosterone supplementation [19].

### Conclusion

Exogenous testosterone use is ever-growing in the adult male population, with or without medical necessity—much of its use being “cosmetic” or enhancing physical performance or sexual gratification, in large part prompted by the media. However, exogenous testosterone supplementation alters testicular biochemistry by suppressing the normal regulatory mechanism of the hypothalamic-pituitary-gonadal axis, with the long-term consequences of azoospermia in men unaffected by age-related infertility. Exogenous testosterone supplementation inhibits intra-testicular testosterone activity, necessary for spermatogenesis.

Patients who take supplemental testosterone in various forms and strengths need to make informed decisions about its use. Clinicians have the responsibility of adequately educating patients and the general public about the undesirable and dangerous side effects of testosterone supplementation, as well as safely using such products when indicated. Furthermore, clinicians can advise patients on other treatment options for any physiological deficits and instruct patients regarding other factors in low testosterone levels, such as stress, diet, and lifestyle, and their impact on the HPG axis. Clinicians should consider culture, geographic region, and socioeconomic status when assessing patients due to distinct variables and statistics.

The long-term use of exogenous testosterone and other androgens adversely affect the HPG axis, resulting in azoospermia and male infertility. However, in most men unaffected by age-related infertility, there is a return of normal spermatogenesis within one year of the discontinuation of exogenous testosterone.

### Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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**Volume 5 Issue 12 December 2020**

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