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Recovery of testosterone following testosterone replacement therapy or antiandrogenic steroid use

Alvin J. X. Zitzmann
Andrology Unit, Klinik Hirslanden, Zurich, Switzerland

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Abstract

The use of testosterone replacement therapy (TRT) for hypogonadism continues to rise, particularly in younger men who tend to remain fertile. Concurrently, assessment of a most prevalent cause of androgen deficiency: androgen deficiency in aging men, has been questioned. Both TRT and AA can suppress gonadotropin secretion and testicular function, which may result in prolonged hypogonadism. Therefore, it is important that clinicians recognize post-TRT or AA use in patients presenting for infertility treatment. Cessation of TRT or AA use may result in spontaneous recovery of normal gonadotropin secretion and testicular function. However, some men may require medical treatment to restore normal gonadotropin or testicular function. Although the evidence is limited, in some cases, clinicians must be aware of the pathophysiologic disengagement of the HPG axis related to TRT or AA use, and the potential for permanent hypogonadism. Although the use of human chorionic gonadotropin, selective estrogen receptor modulators and aromatase inhibitors, all of which are off-label, are poorly described in the literature, potentially creating a knowledge gap for the clinician. Reviewing these pharmacologic options, and the pertinent pathophysiology underlying their use, this review provides a familiarity for the clinician with the manner in which they can be used to recover spermatogenesis after TRT or AA use.

Keywords: androgen, anabolic, hypogonadism, infertility, spermatogenesis, testosterone, testosterone replacement therapy, vasectomy, steroid

INTRODUCTION

In recent years, mass marketing has led to a great public awareness of the age-related decline in serum testosterone levels and the association with hypogonadism with many chronic disease medical comorbidities.[1] This in part has fuelled the growth of testosterone replacement therapy (TRT) for hypogonadism, which has risen in the United States by approximately 400% from 2000 to 2011.[2] This trend accounted for a similar increase in sales where the primary decrease was observed in younger men aged 30 years by 9.444, resulting in an age-group-specific prevalence of 2.1% in 2011.[2] This is not surprising since the prevalence of TRT use in men aged 30–39 years in the United States increased from 0.1% in 2000 to 0.9% in 2011, hypothesized to be attributed to a 750% of 2.7% increase in prevalence of hypogonadism with as many as 12.4% of testosterone prescriptions occurring in men <45 years of age.[2]

Similar to TRT, there has been an increase in the availability and use of anabolic-androgenic steroids (AASs). It is estimated that up to 7 million people use AASs in the United States alone, including up to 75% of men who are in the gym.[3] Although the prevalence of AAS use is unknown, it is thought that many of these estimates are based upon anecdotal data. It is more recent evidence that AAS use is a common cause of pituitary hypogonadism with up to one of five men seeking treatment for hypogonadism having a history of AAS use.[4] Although AAS use is illegal, it is thought to be widely used by many, commonly, amount of hypogonadism.[5] These numbers indicate a concerning shift in the demand for the realm of professional athletics. In addition, many "dietary supplements" tend for athletes or consumers seeking to improve their appearance, have been found to contain AASs.[6] Although, the exact prevalence of MSD of previous AAS abuse remains to be disclosed their particular, with the growing use of AAS, there is a marking a clinician's overall management of the burden of AAS abuse.[7]

Both TRT and AAS use can lead to suppression of the hypothalamic-pituitary-gonadal (HPG) axis, resulting in a deterioration of spermatogenesis and potential infertility. Spermatogenesis recovery in hypogonadism secondary to TRT or AAS use is well described in the literature, with a recent review noting that in middle-aged men, in conjunction with a normal shift toward greater pituitary sensitivity to androgen, to middle-aged men, in conjunction with a normal shift toward greater pituitary sensitivity to androgen, relative to young men, the recovery of spontaneous spermatogenesis and testicular function is achieved in a period of 1–2 years, with no or treatment for hypogonadism with interest in preserving fertility. Meanwhile, men present to infertility specialists for vasectomy reversal (VR) or at average age of 40 years, with a mean duration of vasectomy of 10 years, and a mean number of children of 2.5 years old.[8] Therefore, clinicians need to be keenly aware of the effects of TRT and AAS on spermatogenesis and what treatment options are available to reverse these effects to restore spermatogenesis.

NORMAL HPG AXIS FUNCTION

Normal spermatogenesis is dependent on signaling pathways from the HPG axis. This signaling initially consists of a pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, the initial portal system to the pituitary gland where stimulation results in gonadotropin release. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are released into the systemic circulation and bind to gonadotropin receptors on the testicular Leydig cells (LC) and Sertoli cells (SC), which play an integral role in LC receptor upregulation, steroidogenesis, and maturation.[9,10] Follicle-stimulating hormone (FSH) from the pituitary gland binds to receptors on the SC membrane, initiating spermatogenesis and maintenance of SC function. Maintenance and maturation of high intratesticular testosterone (ITT) concentrations are then necessary in response to LH are critical for normal spermatogenesis to occur.[9,11,12,13] Historically, it was thought that the SC secrete ITT, which then diffuses to the LC and peritubular cells, but more recent data suggest that testicular macrophages are also involved.[14] Interestingly, animal studies have demonstrated that the absence of FSH signaling results in impaired spermatogenesis whereas loss of sufficiently high ITT levels results in the absence of spermatogenesis.[15]

Regulation of the HPG axis occurs via feedback inhibition. Endogenous testosterone directly inhibits GnRH, LH, and FSH secretion, and indirectly inhibits GnRH secretion via its conversion to estrogen, particularly in the hypothalamus. Testosterone also indirectly regulates gonadotropin secretion via estrogen, derived from testosterone conversion peripherally by aromatase enzyme. Estrogen exhibits a dose-dependent effect on the HPG axis, with low levels stimulating GnRH secretion and high levels inhibiting GnRH secretion. Inhibin B levels have consistently correlated with spermatogenesis, for example, men with spermatogenic defects express lower inhibin B levels.[16] Additional activation, inhibition, and modulation of the HPG axis occurs via other hormones, such as prolactin, which inhibits GnRH secretion, or ghrelin, which stimulates GnRH secretion, and neurotransmitters, such as dopamine, gamma-aminobutyric acid, glutamate, serotonin, and TGF-β.[17] Therefore, the HPG axis represents a dynamic, but highly regulated, system of multiple hormones involved in spermatogenesis, among other functions.

INFLUENCE OF EXOGENOUS ANDROGENS ON SPERMATOGENESIS

The use of exogenous androgens influences the HPG axis by similar mechanisms as endogenous testosterone, but extend the resulting negative feedback to a deeper and dendritic dependent fashion, resulting in a reduction in ITT, meaning of FSH production, and ultimately decrease in sustained spermatogenesis. Exogenous androgens can also inhibit the normal function of testicular Leydig cells (LC) and Sertoli cells (SC), resulting in a further decrease in ITT, and ultimately decrease in sustained spermatogenesis. Exogenous androgens can also inhibit the normal function of testicular Leydig cells (LC) and Sertoli cells (SC), resulting in a further decrease in ITT, and ultimately decrease in sustained spermatogenesis. Alternatively, the same data demonstrate a median time to recovery of 20 ± 9.4[18] years ranging from 3 to 41 months, with probabilities, relative recovery increasing from 0.7% 90% to 1.0% 95% and 1.0% 99% at 6, 12, and 24 months respectively. Although, the data suggest that the majority of men will recover, there is a larger exposure to exogenous testosterone, dosage, and other risk may result in a prolonged recovery time to return to normal.[19,20,21,22] Importantly, one must consider that there is no evidence that AAS use results in permanent hypogonadism, although, the duration of AAS use may be prerequisite. Certainly, men with a prolonged history of AAS use may be at greater risk of prolonged recovery time.

AAS are synthetic derivatives of testosterone with chemical modifications intended to enhance the anabolic effects and decrease the adverse effects of testosterone. Many abuses, or "stacking" regimens, combine multiple AAS, in an attempt to achieve the desired effect, while, hopefully, limiting the undesirable side effects. Nevertheless, AAS can still bind the androgen receptor within target cells and exert the same effects as testosterone. Although, the pharmacokinetics of testosterone and AAS are similar, the pharmacodynamics between the two have not necessarily been studied in the literature. Although, it is known that AAS are less a testosterone agonist that AAS is equivalent to urinary preparations and can avoid the hepatical risk of hepatic toxicity, the pharmacodynamics of AAS, therefore, differ from the pharmacodynamics of testosterone, or TRT, in a manner.

Clinically, AAS has proven successful at reducing and/or maintaining spermatogenesis alone or in combination with FSH in patients with hypogonadotropic hypogonadism.[23,24] Although, it is not necessary for treatable cause of male factor infertility clinically considered secondary to pathology of the hypothalamus or pituitary gland, AAS use, or TRT use, is a cause of male factor infertility secondary to pituitary adenoma, craniopharyngioma, or radiation, or idiopathic causes.[25] Recently, recognized the increasingly common use of exogenous TRT and/or AAS use and other HPG axis factors or adrenal, HPA axis, or other hormonal factors, which may result in a prolonged recovery time to return to normal, or, in some cases, to a state of hypogonadism, which, in turn, may result in a clinician's efforts to optimize the HPG axis prior to spermatogenesis. Alternatively, there, due to the uncommon prevalence of MSD, hypogonadism may be lasting and may not achieve normal sperm and spermatogenesis.[26,27]

Historically, treatment approaches for MD have focused upon gonadotropin, particularly GnRH therapy to stimulate endogenous testosterone production and spermatogenesis, and, more recently, the use of aromatase inhibitors (AIs) to increase endogenous testosterone production and improve sperm parameters.[28] However, subsequent reviews of clinical trials, and, improvement of a functionally intact pituitary gland to respond to GnRH stimulation, have shown that GnRH therapy is ineffective in patients with hypogonadotropic hypogonadism, particularly, in patients with prolonged duration of hypogonadism, or, in patients with a history of exogenous testosterone based upon a recent meta-analysis.[29] Therefore, gonadotropin alone, particularly, in patients with prolonged duration of hypogonadism, or, in patients with a history of exogenous testosterone has proven unsuccessful at inducing spermatogenesis or normalizing testicular function. Alternatively, the use of human chorionic gonadotropin (hCG) 1500 IU, and follicle-stimulating hormone (FSH) 75 IU, administered twice weekly, has been shown to be effective in restoring spermatogenesis, fertility, and testicular function in men with secondary hypogonadism.[30] Although, the use of hCG and FSH, in conjunction with AIS, has demonstrated improvement in testicular function, and, in some cases, improvement in spermatogenesis, the use of hCG and FSH, in conjunction with AIS, has not been shown to be effective in restoring spermatogenesis, fertility, and testicular function in men with secondary hypogonadism.[31] Although, the use of hCG and FSH, in conjunction with AIS, has not been shown to be effective in restoring spermatogenesis, fertility, and testicular function in men with secondary hypogonadism.[32] Although, the use of hCG and FSH, in conjunction with AIS, has not been shown to be effective in restoring spermatogenesis, fertility, and testicular function in men 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