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REVIEW

Anabolic steroid misuse and male infertility: management and strategies to improve patient awareness

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ABSTRACT

Introduction: Anabolic androgenic steroid use is an uncommon but important cause of male infertility. As paternal age and anabolic steroid use increases, providers are more likely than ever to encounter men with infertility and prior or concurrent anabolic steroid use. In this review, we outline the background, epidemiology and pathophysiology of anabolic steroid induced male infertility and provide recommendations regarding the diagnosis, management, and future prevention of this condition.

Areas covered: Male reproductive physiology is a tightly regulated process that can be influenced by exogenous sources such as anabolic steroids and selective androgen receptor modulators (SARMs). Data suggest that a combination of selective estrogen receptor modulators (SERMs), human chorionic gonadotropin (hCG), aromatase inhibitors (AIs), and recombinant follicle-stimulating hormone (rFSH) may lead to spermatogenesis recovery.

Expert opinion: Anabolic steroid and SARM users continue to exhibit lack of understanding regarding the potential side effects of their use on male fertility. Current literature suggests that spermatogenesis can be safely recovered using a combination of SERMs, hCG, AIs and rFSH although additional studies are necessary. While anabolic steroid prevention strategies have largely been focused on the individual level, further investigation is necessary and should be approached in a socioecological manner.

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Anabolic androgenic steroids; clomiphene citrate; human chorionic gonadotropin; hypogonadism; male infertility; selective androgen receptor modulators; selective estrogen receptor modulators; spermatogenesis; testosterone; testosterone replacement therapy

1. Introduction

Functional male testes and an intact hypothalamic-pituitary-gonadal (HPG) axis are essential for normal male fertility and adequate testosterone production. This process is maintained through precise coordination of stimulatory hormones and negative feedback mechanisms. Any disruption in this pathway can lead to male hypogonadism and dysfunction of spermatogenesis. Anabolic androgenic steroids (AAS) are synthetic derivatives of testosterone that were initially researched in the 1930s and are approved for a variety of conditions such as testosterone deficiency, osteoporosis, breast cancer, delayed puberty, and cachexia [1]. Despite having a therapeutic role in medicine, AAS are commonly abused by men to achieve supraphysiologic androgen levels and increase muscle mass. In fact, AAS use is currently on the rise with a worldwide prevalence as high as 6.4% [2]. This is concerning and likely related to a growing preoccupation and obsession among men with obtaining a muscular physique, commonly referred to as the 'Adonis complex' and 'bigorexia' [3,4]. While AAS have desired effects on muscle growth, strength gains, and fat loss, their use is not without risk. AAS use can lead to acne, hair loss, gynecomastia, hepatic dysfunction, hypogonadism, male infertility and has been linked with cardiovascular disorders and even premature death [5–8]. AAS use is known to cause male infertility via suppression of the natural HPG axis, but there appears to be limited data regarding management of AAS induced infertility. In this review, we outline the background and epidemiology of AAS and patient motivations for AAS use, summarize the pathophysiology of AAS induced male hypogonadism, and provide treatment recommendations and strategies for AAS induced male infertility.

2. Male reproductive physiology

Male reproductive function is a finely tuned process that requires exact coordination of the HPG axis via stimulatory release of hormones and feedback inhibition. A functional HPG axis is essential for normal testicular function, including normal male fertility and testosterone production. This process begins with the hypothalamus which is positioned at the base of the brain and lies just above the optic chiasm and pituitary gland. The hypothalamus is directly linked to the pituitary gland which lies within a depression at the base of the skull called the sella turcica. The pituitary gland is composed of two separate distinct structures, the adenohypophysis (anterior pituitary) and neurohypophysis (posterior pituitary). The anterior pituitary is responsible for synthesizing and secreting peptide hormones such as adrenocorticotropin, gonadotropins, prolactin, growth hormone, and thyroid-stimulating hormone. The posterior pituitary does not synthesize hormones but rather stores and releases vasopressin and

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Article highlights

- Anabolic androgenic steroid use is an important cause of male infertility that physicians should be aware of.
- The hypothalamic pituitary gonadal axis is a finely tuned process that is easily influenced by exogenous anabolic steroid use which leads to impaired spermatogenesis and male infertility.
- The majority of anabolic steroid users are unaware of the fertility side effects associated with its use.
- Chronic anabolic steroid use has been linked with myocardial infarction, cardiomyopathy, accelerated atherosclerosis, stroke and premature death.
- Anabolic steroid users can be categorized into four separate groups: the YOLO (You Only Live Once) type, the Athlete type, the Well-Being type, and the Expert type.
- A growing preoccupation on male body image and increasing social media use among men may contribute to the rising prevalence of anabolic steroid use.
- Selective androgen receptor modulators are a new class of performance and image enhancing compounds being misused by men and can have similar side effects of hypogonadism and male infertility.
- While data regarding the management of anabolic steroid induced infertility is limited, studies suggest that the use of SERMs (clomiphene citrate), hCG, anastrozole, and rFSH may have success with spermatogenesis recovery although some patients may experience permanent dysfunction of the HPG axis following steroid use.

Although anabolic steroid prevention tactics have been enacted, the prevalence of steroid use appears to be on the rise. Future prevention efforts may be more successful if a socioecological approach is utilized, targeting not just individuals but multiple ecological levels including social network, institutional, community and societal.

oxytocin which are synthesized by neurosecretory cells of the hypothalamus. The hypothalamus is connected to the anterior pituitary via neuronal pathways and portal vasculature which allow for direct, pulsatile delivery of hormones, such as gonadotropin-releasing hormone (GnRH), to the anterior pituitary. GnRH secretion is influenced by a multitude of factors such as diet, exercise, stress, higher brain centers, pituitary secreted gonadotropins and circulating gonadal hormones. Modulators of GnRH secretion include opioids, catecholamines, sex steroids (testosterone), prostaglandins, insulin and kisspeptins. GnRH secretion is known to peak every 90 to 120 minutes, during the early morning hours and during the spring months. Once released, GnRH has an approximate half-life of five to seven minutes and stimulates the synthesis of gonadotropins such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. LH and FSH are the primary regulators of testicular function. In the testicle, LH stimulates the Leydig cells to convert cholesterol to pregnenolone and testosterone while FSH stimulates the Sertoli cells within the seminiferous tubules and regulates spermatogenesis in adults. The testicles also produce the hormones, inhibin and activin. Inhibin is a protein hormone that is released by the Sertoli cells through FSH stimulation. Inhibin acts on the hypothalamus and pituitary via a negative feedback mechanism to inhibit the release of FSH. Similarly, activin is a protein hormone which is released by the Leydig cells and stimulates FSH secretion [9]. The HPG axis, including the inhibitors and stimulators, is further outlined in Figure 1.

2.1. Role of testosterone

Testosterone is the most potent naturally occurring androgen and the original AAS. Testosterone levels range from 300 to 1000 ng/dL in the adult male and progressively decline with age. Testosterone is primarily produced within the testes by the Leydig cells, although a small amount is secreted by the adrenal gland. The physiologic effects of testosterone can be categorized as 'androgenic' and 'anabolic'. Androgenic effects include the induction of secondary male sex characteristics such as facial and body hair growth, sebaceous gland activity, and the maturation of sperm and libido. Anabolic effects involve nitrogen retention, protein and collagen synthesis and an increase in muscle size and bone metabolism. Nitrogen is a unique component of amino acids and its excretion can be used to directly measure the body's muscle building potential. Testosterone promotes a positive nitrogen balance through protein synthesis and inhibition of protein degradation. These effects play a key role in maximizing muscle growth. While testosterone is known to have anti-catabolic effects via glucocorticoid inhibition, it is mainly the anabolic effects that are of interest for AAS users. To exert its physiologic effects, testosterone penetrates the cellular membrane and binds to the intracellular androgen receptor. This receptor-hormone complex then relocates to the nucleus to induce gene transcription and protein synthesis. In the nonclassical pathway, testosterone stimulation results in direct activation of downstream kinases, transcription factors, and cell depolarization although this process is still poorly understood [10,11]. Additionally, testosterone may be converted into dihydrotestosterone (DHT) by 5α-reductase in the scalp, liver, prostate, and testicles. DHT has an increased affinity for the androgen receptor and plays a role in maturation of the penis and scrotum during puberty, facial, body and pubic hair growth, and development and maintenance of the prostate and seminal vesicles. DHT is essential for normal erectile function and libido but can also have unwanted androgenic effects such as benign prostatic hyperplasia, hair loss, and acne. Finally, testosterone can be aromatized to estradiol which exerts estrogenic effects including breast tissue growth, water retention, and increased body fat deposition. There is a significant amount of aromatase located within adipose tissue which can lead to increased estrogen levels often seen in obese men.

3. Anabolic androgenic steroids

As previously outlined, the physiologic effects of testosterone can be categorized as anabolic and androgenic. AAS exert very similar physiologic effects to that of testosterone given their almost identical mechanism of action. Typically, the greater the anabolic effect of a steroid, the weaker the affinity for the androgen receptor and less of an androgenic effect. Alternatively, steroids that bind strongly to the androgen receptor will exert a more potent androgenic effect and less of an anabolic effect. While most AAS exert both anabolic and androgenic effects, none are completely selective. To assess and quantify the relative potency of AAS, a myotrophic-

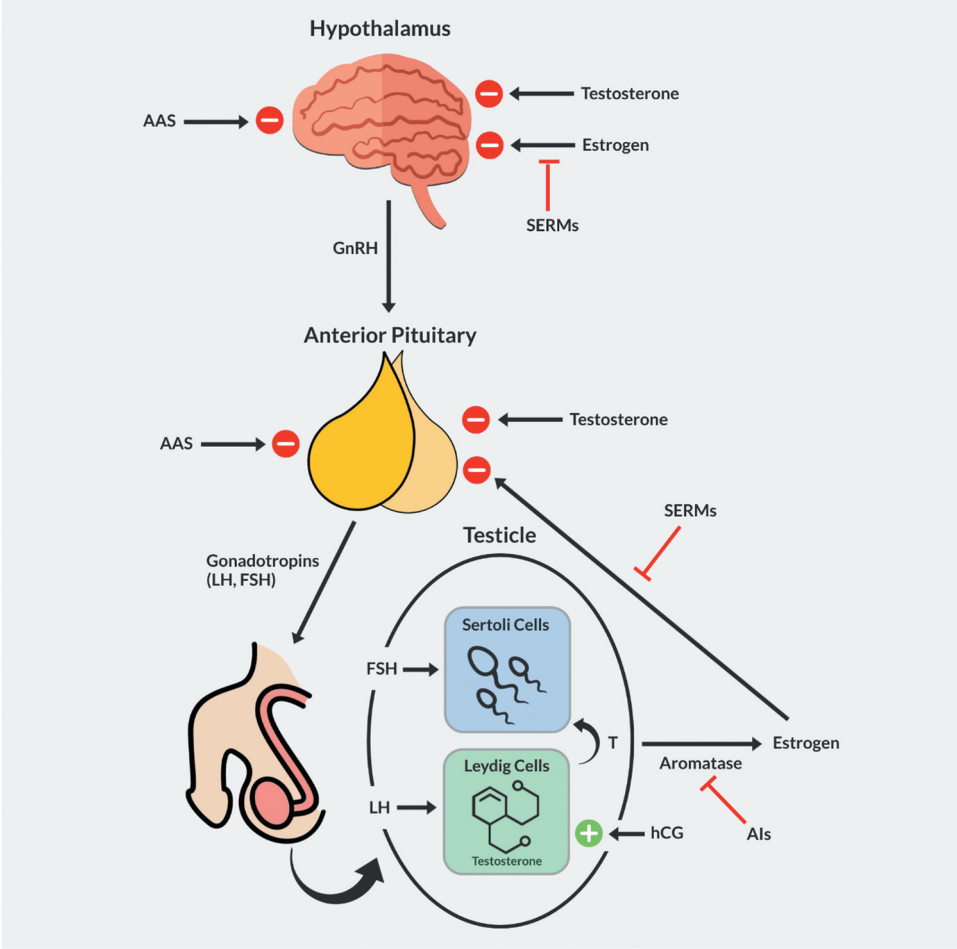

Figure 1. The HPG axis including the mechanism of action of inhibitors and stimulators. AAS: anabolic androgenic steroids, GnRH: gonadotropin releasing hormone, SERMs: selective estrogen receptor modulators, LH; luteinizing hormone, FSH: follicle-stimulating hormone, hCG: human chorionic gonadotropin, AI: aromatase inhibitors.

androgenic (MA) index was developed. The MA index compares a steroid's anabolic and androgenic effects relative to that of testosterone. Researchers analyzed the effects of steroids on rat levator ani muscle weight (anabolic effect) and rat seminal vesicles or prostate weight (androgenic effect). Multiple substances were tested and assigned varying degrees of anabolic:androgenic potential relative to testosterone. Testosterone, being the fundamental AAS, was assigned a MA index of 1:1. While this study was performed over 70 years ago and may have several critiques given the in vivo nature of the experiment, it provides better insight into the activities and effects of many AAS [12].

Regardless, use of AAS disrupts the natural HPG axis in a similar mechanism as exogenous testosterone and leads to hypogonadotropic hypogonadism via inhibition of pulsatile GnRH release. This subsequently leads to a decrease in FSH and LH which results in a decrease in intratesticular testosterone (ITT) and overall testosterone production. ITT is essential for normal spermatogenesis and its inhibition can lead to azoospermia [13,14]. ITT suppression can lead to permanent testicular dysfunction, hypogonadism, and infertility. The duration of HPG axis suppression is highly variable and is dependent upon multiple factors including the differences in the choices of AAS, quantity used, and duration of use. Spermatogenesis typically recovers after 4–6 months after discontinuation of AAS but can take as long as 3 years to return. In some cases, the HPG axis may never fully recover, and the patient may have permanent dysfunction of the HPG axis [15–17]. Some studies suggest that younger men may have a higher likelihood of HPG axis normalization following AAS cessation [18]. It is likely that younger men with higher baseline testosterone levels and shorter duration of low dose AAS use are more likely to quickly and completely recover GnRH pulsation and gonadotropin secretion when compared to older AAS users due to a more 'elastic' HPG axis. The deleterious effects of AAS on testicular function and male fertility are well documented and cannot be overstated [19,20]. In fact, one study demonstrated that the number one regret among AAS users was the lack of understanding regarding the implications of AAS use on future fertility [21].

Over time, modifications have been made to the chemical structure of testosterone to maximize the anabolic effects and minimize the androgenic effects. These structural modifications influence a compound's bioavailability, pharmacokinetics, and the balance of anabolic to androgenic activity. AAS include the synthetic derivatives of testosterone in addition to testosterone

itself. Exogenous testosterone is available in an injectable form, subcutaneous pellets, transdermal patch, topical skin cream, and a newly approved oral softgel preparation. The synthetic derivatives of testosterone are traditionally classified into two categories based on their route of administration and carrier solvents. Oral AAS (17α-alkylated derivatives) resist hepatic first-pass metabolism and remain orally active. These compounds typically have short half-lives; therefore, several daily doses are necessary to maintain adequate serum concentrations. It is prudent to monitor hepatic function given the risk of significant hepatotoxicity. Examples of 17α-alkylated compounds include methyltestosterone, methandrostenolone, norethandrolone, fluoxymesterone, danazol, oxandrolone and stanozolol. Parenteral AAS (17β-esterified derivatives) typically have a longer half-life and slower absorption rate, leading to much less risk for hepatic dysfunction. Esterification of the testosterone molecule results in increased fat solubility and delayed absorption into the circulation. Examples of 17β-esterified derivatives include testosterone bound to esters such as cypionate, propionate, enanthate, and undecanoate, nandrolone (19-nortestosterone), which has a very favorable anabolic to androgenic profile, boldenone and trenbolone.

Some propose an AAS classification system based upon the desired effects [22]. Compounds that exert a more balanced anabolic:androgenic profile are termed "testosterone-like' as testosterone exhibits a MA ratio of 1:1. These include testosterone esters, methyltestosterone and methandrostenolone. Compounds that demonstrate a more potent androgenic effect are coined 'DHT-like' molecules due to their resemblance to DHT and the inability to be aromatized to estrogen. These include stanozolol and oxandrolone. Finally, compounds with the highest anabolic activity and least androgenic potency are termed 'nandrolone-like' molecules. Examples include nandrolone esters and trenbolone. Nandrolone, or 19-nortestosterone, has gained popularity due to its highly desired anabolic:androgenic profile. Its 5α-reduced metabolite has poor androgen receptor affinity which explains its higher anabolic potential and low androgenic potency. In addition, nandrolone avoids aromatization and lacks the feminizing side effects of testosterone.

3.1. Background and epidemiology

The exogenous use of testosterone for the restoration of strength and vitality is well documented and was initially, albeit crudely, described in 1889 by an aging Dr. Brown-Sequard after self-injection of canine testicular extract led to a reported improvement in his physical strength, mental qualities, and appetite. Although later studies were unable to replicate these findings, this claim sparked an interest in the field of organotherapy which subsequently led to the discovery and isolation of testosterone from bull testes by Dr. Ernst Laqueur in 1935 [23]. There have been significant advances in the field of hormone replacement therapy throughout the years, most notably after the advent of synthetic androgens. Synthetic AAS have been FDA-approved for a variety of medical conditions including testosterone deficiency, osteoporosis, breast cancer, delayed puberty, and cachexia [1]. While synthetic androgens certainly have their appropriate therapeutic role, the recreational and nonmedical use of AAS has rapidly evolved since their creation. Commonly used AAS are outlined in Figure 2 and include oral oxandrolone (Oxandrin, Anavar), oral methandienone (Dianabol), injectable stanozolol (Winstrol), injectable nandrolone decanoate (Deca-Durabolin), and injectable boldenone undecylenate (Equipois) [24].

While nonmedical AAS use is typically associated with bodybuilders and athletes, there is an ever-growing increase of AAS use among men seeking to achieve an optimal and aesthetic male physique. In fact, four out of five AAS users are not competitive athletes but rather men seeking to achieve an 'enhanced' physical appearance [25–28]. In an excellent review, Christiansen and colleagues proposed a unified framework categorizing the type of AAS users. This typology consists of four groups of AAS users: the Expert type, the Well-Being type, the YOLO (You Only Live Once) type, and the Athlete type [29].

Since the 'golden age' of AAS research in the 1950s and 1960s, the recreational use of AAS has rapidly grown to become a true public health concern. Worldwide, the lifetime prevalence of AAS use is estimated to be 3.3%, with a higher prevalence among males (6.4%). Studies also suggest that nearly one-third of AAS users will develop dependence [2]. Even more alarming, an estimated 15%-30% of male gym goers are users of AAS [25,30]. In addition, there was noted to be a growing trend of androgen replacement therapy within specialty men's health and rejuvenation clinics [1]. Unfortunately, these trends continue to worsen [22]. While the prevalence of recreational AAS use among adolescents has steadily declined over the last 20 years, likely due to the success of AAS education and prevention campaigns targeting high school athletes in the 1990s, there appears to be increasing popularity of AAS use among young adult men in their 20s-30s [31–33]. A recent comprehensive review estimated that 2.9 to 4 million Americans may have previously used AAS with AAS dependance developing in up to 30% of these patients. The average age of first AAS use was 22 and only 22% of AAS users endorsed use prior to age 20 [5]. An additional study suggests that the majority of AAS users are white, of slightly above average socioeconomic status and self-reported as perfectionists and highly goal oriented [26].

3.2. Patient motivations and bigorexia

There continues to be a growing focus on male body image, especially with increasing social media usage. Men have demonstrated a growing preoccupation and obsession with achieving a 'perfect' and muscular physique, what Pope originally described as the 'Adonis complex' [3]. This pathological preoccupation with muscularity and leanness is a relatively new body image disturbance that predominantly affects men. In fact, the primary motivation among AAS users is to improve appearance and gain muscle [34]. Commonly referred to as 'bigorexia,' this pathologic fixation on muscle growth and appearance is officially recognized by the DSM-5 as a body dysmorphic disorder [4]. The crisis of male body obsession originally began in the 1970s to 1980s through proliferation of muscular male bodies in movies, television programs, fitness magazines, and advertising.

Compound Name	Brand Name
Testosterone-Like Effects	
Testosterone esters: cypionate	Deposteron®, Testex Leo®
Testosterone esters: undecanoate	Nebido®, Androxon®
Testosterone esters: blends	Durasteston®, Testoviron®, Sustanon®, Omnadren®
Methyletestosterone	Methyltestosterone®, Metandren®
Methandrostenolone	Dianabol®, Ananbol®, Naposim®
Chlorordehydromethyltestosterone	Turinabol®
Fluoxymesterone	Halotestin®
Boldenone	Equipoise®, Equilon®
DHT-Like Effects	
Stanozolol	Winstrol®, Stromba®
Oxandrolone	Anavar®
Oxymetholone	Anadrol®, Hemogenin®, Anapolon
Mesterolone	Proviron®
Methenolone	Primobolan®
Nandrolone-Like Effects	
Nandrolone decanoate	Decadurabolin®
Nandrolone phenylproprionate	Durabolin®
Trenbolone	Finaplix®, Parabolin®
Nandrolone undecanoate	Dynabolon®

Figure 2. Commonly used anabolic androgenic steroids grouped according to effect. DHT: dihydrotestosterone.

This fixation on body image is even more apparent today due to increasing social media use and a constant state of being 'plugged-in' to media through home streaming, cell phone and personal computer usage, etc. This drive for masculinity and the desire to achieve a 'super-hero' like physique reflects cultural changes in male body ideals and the increasing societal pressure for men to possess a muscular body. It is no surprise there is a body crisis among men, especially given the rise of fitness 'influencers' on social media who promote their physique daily to their online followers. Multiple studies have demonstrated that exposure to social media can lead to body dissatisfaction and eating disorders through various mechanisms, including physical appearance comparisons and self-objectification [35,36]. One study examined social media usage among 2700 men and found a positive association between image-centric social media platforms (i.e. Instagram, Snapchat and Facebook) and body dissatisfaction, eating disorder symptoms and thoughts of using AAS to improve their physical appearance [37]. It is important to recognize that men have never felt more societal pressure to have a muscular and lean physique than now which likely contributes to the increasing prevalence of AAS use.

3.3. The good, the bad, and the ugly

The physiologic effects of testosterone and synthetic AAS are well documented and include an increase in erythropoiesis, lipolysis, protein synthesis, libido, and anti-catabolic effects via an anti-glucocorticoid mechanism. However, the increase in muscular activity via skeletal muscle hypertrophy is the main effect of AAS use and the primary motivation for AAS use among men. While the benefit of AAS in restoring normal androgen levels and increasing muscle mass in hypogonadal men is well established, the perceived benefit of AAS in eugonadal men remained unsubstantiated and was hotly contested for decades until the release of a landmark study by Bhasin and colleagues in 1996. This randomized, controlled, and blinded trial assigned 43 men to one of four groups: placebo with no exercise, testosterone with no exercise, placebo plus exercise and testosterone plus exercise. Men receiving androgenic steroids were administered weekly injections of 600 mg testosterone enanthate for 10 weeks. Fat-free mass, muscle size, and upper/lower body strength were measured before and after the treatment period. The men assigned to the testosterone with exercise group had far greater and significant increases in all three categories when compared to either no exercise group. This study validated the claim that supraphysiologic doses of testosterone, especially when combined with exercise, increase fat-free mass and muscle size in eugonadal men [38]. Large-scale surveys sampling AAS users via online bodybuilding forums found that the most common motivations for starting AAS were to increase muscle mass and decrease body fat [25,26]. Of note, men also felt the need to continue their regimens due to possible muscle mass loss, fat gain, and excessive hypogonadal symptoms following AAS cessation.

When compared to most drug abusers, AAS users demonstrate considerable forethought into their substance abuse [33]. AAS users typically gather all the necessary supplies and medications prior to beginning their 'treatment' regimen. Most AAS users adhere to a strict regimen consisting of 'stacking' and 'cycling'. Large doses of differing oral and injectable compounds are combined (stacked) and self-administered during periods (cycles) lasting 4–12 weeks. The goal of stacking is to combine multiple compounds with varying levels of anabolic:androgenic potential to avoid overlap of benefits and side effects. In addition, lower doses of multiple agents have a theoretical lower risk of adverse effects when compared to larger doses of a single compound. This also avoids a 'plateauing' effect by slowly achieving supraphysiologic doses over a longer period. Another common technique is gradually tapering at the beginning and end of a cycle, referred to as a 'pyramid,' rather than abruptly starting and stopping a cycle. Classically, AAS users may combine 'mass building stacks' (testosterone and nandrolone) with 'cutting stacks' (oxandrolone and stanozolol) to maximize muscular and strength gains and minimize salt, water, and fat retention, respectively. It is also common for AAS users to finish their cycles with human chorionic gonadotropin (hCG) or anti-estrogens to kickstart androgen production, commonly referred to as 'post-cycle therapy' or 'PCT' [22].

While AAS can certainly produce desired effects, their use is not without risk. The adverse effects of AAS are well documented and include acne, hair loss, prostatic enlargement which can lead to lower urinary tract symptoms, gynecomastia, hepatic dysfunction, in addition to erectile dysfunction and decreased libido following AAS cessation [39]. Of note, there is emerging evidence that implicates long-term AAS use with several adverse health effects including increased risk of cardiovascular disorders, premature death, psychiatric effects, and prolonged suppression of the HPG axis. In fact, one study suggests that the mortality risk is 4.6 times higher in chronic AAS users vs non-users [40]. Long-term exposure to supraphysiologic doses of AAS has been linked with myocardial dysfunction, stroke, clinically significant cardiomyopathy, and acceleration of atherosclerotic disease. Currently, there is no substantial evidence that testosterone therapy, when replaced to normal levels, increases the risk for cardiovascular events although there is a growing number of case reports and small series that suggests supraphysiologic levels associated with AAS may increase cardiovascular risk. [41–51] AAS users may also experience hypomanic or manic symptoms, which can be associated with aggression, violence and even homicide. AAS may be psychologically addictive as withdrawal and dependency disorders have been reported. Acute anabolic steroid withdrawal may produce physical withdrawal symptoms similar to opiate withdrawal which include anxiety, irritability, hot flashes, and insomnia [6–8,52].

4. Selective androgen receptor modulators: the new kid on the block

Another growing area of concern is the increasing use of selective androgen receptor modulators (SARMs) among AAS users and bodybuilders. SARMs were initially researched in the 1940s, but it was not until the late 1990s that the modern SARM era was encountered after scientists with Ligand Pharmaceuticals and the University of Tennessee developed a novel series of cyclic, nonsteroidal quinolinones which demonstrated anabolic activity on skeletal muscle with varying degrees of tissue selectivity [53,54]. These modulators differentially bind to androgen receptors and result in anabolic cellular activity while avoiding many of the traditional side effects of AAS. While there are typically less systemic side effects noted with SARMs, these compounds affect the HPG axis in a similar fashion as AAS and can lead to suppression of LH, FSH, testosterone production, and spermatogenesis [55]. Although there are currently no FDA-approved indications for these compounds, early clinical studies have demonstrated potential uses for cancer-related cachexia, muscle wasting disorders, BPH, hypogonadism and breast cancer [55,56]. As expected, these compounds are of interest to the bodybuilding community due to their anabolic potential, lack of androgenic side effects and oral bioavailability. Unfortunately, many SARMs are readily available for purchase online despite having no FDA approved indications, although research suggests that most of these products may not be reliable. Van Wagoner and colleagues found that among 44 products marketed and sold online as SARMs, only 52% actually contained SARMs and many were inaccurately labeled or contained unapproved drugs and substances [57]. The most popular SARMs on the market include Ostarine (MK-2866), Ligandrol (LGD-4033), Testolene (RAD140), and Andarine (GTx-007, S-4) [58,59]. To combat the widespread distribution of these new compounds, Chinese lawmakers recently passed legislation banning the production and exportation of SARMs [60]. In addition, American legislators have introduced the SARMs Control Act of 2019 which will place SARMs within the same class as anabolic steroids, making their sale illegal [61].

4.1. Cardarine and MK-677

It is also important to note that AAS and SARM users frequently combine multiple substances to enhance their performance, such as insulin, growth hormone, stimulants, aromatase inhibitors, opioids, and diuretics [22]. In fact, there appears to be growing popularity of two particular substances within the fitness community, Cardarine (GW 501516) and MK-677 (Ibutamoren). These compounds are typically grouped together as SARMs by the bodybuilding community despite being endurance supplements with separate mechanisms of action. Cardarine is a peroxisome proliferative activated receptor-omega agonist that regulates muscle metabolism, improves cardiovascular output, and enhances training endurance. Activation of the receptor increases fat-burning capacity and muscle production and adjusts the body's fuel preference from glucose to lipids [62]. There is currently no clinical use for this compound. In fact, drug development was abandoned after abstracts reported rapid induction of cancer in mice models. This led to warnings being issued by the World Anti-Doping Agency which stated that 'serious toxicities' were discovered in preclinical studies and that clinical approval would never be granted for this substance [63]. Despite these warnings, cardarine continues to be frequently abused for its performance enhancing potential. MK-677 is an oral non-steroidal growth hormone secretagogue and ghrelin receptor agonist that increases secretion of growth hormone and insulin-like growth factor 1 (IGF-1). This leads to an increase in muscle mass while avoiding suppression of native testosterone production [58,64]. MK-677 has been studied for clinical use in patients with growth hormone deficiency and sarcopenia and shows clinical promise, although it is frequently abused by bodybuilders and fitness enthusiasts for its muscle building potential and ease of administration [65].

5. Effects of anabolic steroid use on spermatogenesis

AAS use is an important cause of male infertility and should always be on the differential when men present with fertility complaints. Most patients are rarely forthcoming with physicians regarding their AAS use. In fact, in a recent large-scale survey of 2,385 AAS users, 56% of patients had never disclosed their AAS use to their health-care provider. This is concerning, but not surprising, as 55% of users who did disclose their AAS use reported feeling discriminated against for their use [34]. Given the growing use of testosterone replacement therapy (TRT) and AAS use among young to middle aged men, in addition to rising average paternal age, physicians are increasingly likely to

encounter men seeking treatment for infertility related to prior TRT and AAS use [21]. Providers must be aware of the potential fertility side effects of AAS and conduct a detailed but objective history in a non-judgmental fashion to elucidate this information. It should also be noted that advanced paternal age has been linked with an increased risk of adverse health outcomes in offspring due to higher rates of de novo germline mutations, sperm aneuploidy, chromosomal abnormalities, birth defects and genetic conditions such as chondrodysplasia, schizophrenia, and autism [66]. The combined effects of advanced paternal age and AAS use on fertility and offspring health outcomes are currently unknown.

As previously described, exogenous testosterone and AAS inhibit the natural HPG axis which leads to hypogonadotropic hypogonadism, decreased serum testosterone levels, decreased ITT levels and testicular atrophy. While these effects are well described in the literature, a recent survey demonstrated that an alarming 25% of clinicians used exogenous testosterone as empiric treatment for idiopathic male infertility [67]. An adequate ITT concentration is essential for normal spermatogenesis, therefore, addressing the underlying hypogonadism is the most important aspect in restoration of ITT levels and management of AAS-induced male infertility [19,68]. Infertility following AAS use can present with a multitude of semen analysis abnormalities, such as oligozoospermia, azoospermia or defects in sperm motility and morphology [69]. Animal models revealed that AAS exposure can lead to Leydig cell alterations, decreased LH and testosterone levels, reduced population of Leydig cells, and significant end-stage impairments to spermatogenesis with lack of advanced spermatids. While Leydig cells tend to proliferate after AAS cessation, their counts remain below normal, even after longer periods [70,71]. AAS use may also affect semen quality, as studies suggest abnormal and hypokinetic sperm may persist despite restoration of normal spermatogenesis following hCG stimulation [72]. Finally, there appears to be an association between AAS use and germ cell apoptosis in addition to anomalies within the meiotic process [18,73].

Studies suggest that AAS-induced oligozoospermia and azoospermia typically resolve after 4–12 months, although the negative effects on semen quality may persist for longer or indefinitely [17]. One large-scale study examined the reversibility of hormonal male contraception and found that 67% of men recovered spermatogenesis within 6 months, 90% within 12 months, and 100% within 24 months [74]. In fact, some argue for conservative management of AAS-induced azoospermia with reservation of medical therapies until after 24 months given the chance of spontaneous recovery. While spermatogenesis recovery time appears to be highly variable among patients, some data suggest that increasing age and duration of use appear to significantly reduce the likelihood of spermatogenesis recovery [75].

6. Treatment strategies for anabolic steroid induced infertility

While this review is focused on the management of AAS induced infertility, the clinician should be aware of the basic infertility work up. An infertility evaluation should be offered to any male with an unsuccessful pregnancy after one year of unprotected sexual intercourse, risk factors for infertility or questions regarding their fertility potential. The initial screening assessment should include a detailed reproductive history and two semen analyses (SA) separated by a period of at least one month [76]. The physical exam is integral in the evaluation of the infertile male and can reveal anatomic abnormalities such as a varicocele or congenital bilateral absence of the vasa deferens. FSH and testosterone levels should be assessed in men with moderate oligozoospermia and Y-chromosome microdeletion analysis and karyotype should be obtained in men with severe oligozoospermia (<5 million sperm/mL). LH and estradiol levels may also be of benefit. Those with azoospermia and SA findings suggestive of ejaculatory duct obstruction should receive a transrectal ultrasound.

Patients with AAS induced infertility may present with a remote history of AAS use or with concurrent AAS use. Some users may seek treatment and assistance with permanent discontinuation of AAS. If permanent cessation is desired, certain steps must be taken. Once the diagnosis of AAS induced infertility is made, the first and most important step is AAS discontinuation. After the clinician has established a healthy and non-judgmental relationship with the patient, the patient must be encouraged to stop all AAS use, preferably in a tapered manner to avoid withdrawal symptoms. A short 4-week tapered course of injectable or transdermal TRT may be offered to those with severe symptoms following AAS cessation [19]. Fortunately, there are options to restore the HPG axis in men with AAS induced infertility via a combination of gonadotropin analogs (hCG and recombinant FSH), selective estrogen receptor modulators (SERMs), and aromatase inhibitors (AIs).

6.1. hCG and FSH

Human chorionic gonadotropin (hCG) is a naturally occurring hormone that is produced by the human placenta and found in the urine of pregnant females. hCG plays a prominent role in the maintenance of early pregnancy but can also be derived from recombinant sources. Structurally, hCG is composed of an α and β-subunit which closely resemble that of LH. LH and hCG share an identical α-subunit while the β-subunit of hCG is essentially the same except for an additional highly glycosylated 24 amino acid tail. This subtle difference leads to increased receptor activity and slower metabolism (half-life 36 hours) when compared to LH (half-life 30 min), making it an ideal LH analog. hCG has shown promise in restoration of spermatogenesis and is an effective option for AAS users who wish to regain fertility quickly [74,77]. Similarly, FSH has been derived from the urine of postmenopausal females in the form of human menopausal gonadotropin (HMG). HMG largely consists of copurified urinary proteins inactive at the FSH receptor with the remainder being blend of FSH, LH, and hCG. To achieve higher FSH receptor selectivity, refinements led to the production of a highly purified urinary HMG in addition to a recombinant FSH (rFSH). Despite there being limited data comparing the two, rFSH is typically preferred due to the theoretical risk of HMG related prion disease [78].

While the success of gonadotropins at inducing or maintaining spermatogenesis in patients with classic hypogonadotropic hypogonadism is well established, there is a scarcity of evidence specifically regarding the role of gonadotropins in men with TRT/AAS induced azoospermia [79]. Despite this paucity of data, studies show promising results. A recent multi-institutional study examined the effects of hCG on spermatogenesis in men with azoospermia or severe oligozoospermia and prior testosterone use. These researchers found that administration of 3,000 IU of hCG every other day paired with clomiphene citrate, tamoxifen, anastrozole, or rFSH led to recovery of spermatogenesis in 98% of patients. The average time to first sperm recovery or improvement above 1 million/mL was 4.6 months with a mean first sperm density of 22.6 million/mL [80]. FSH given alone or in combination with testosterone has proven to be unsuccessful at recovery of spermatogenesis. However, there appears to be a role for FSH as an adjunct to hCG. Studies revealed that the addition of FSH to hCG results in even further improvement in spermatogenesis than hCG alone and suggests a timelier recovery with both gonadotropins. However, it is important to recognize that most of this data is regarding men with hypogonadotropic hypogonadism due to classic causes and not prior TRT/AAS use. There are even less studies specifically examining gonadotropins and AAS induced azoospermia, although case reports indicate that hCG alone or combined with FSH can restore spermatogenesis in this population [15,17,81,82]. When analyzed collectively, these reports suggest that restoration of spermatogenesis using gonadotropins is a successful strategy in patients with prior AAS use. Most treatment regimens consist of starting hCG at doses of 1,500 to 5,000 IU 2–3 times per week for 3–6 months. If there is no improvement in spermatogenesis on hCG alone, rFSH can be added at doses of 75 to 400 IU 2–3 times per week [78].

It is also important to note that hCG can be used to maintain spermatogenesis while simultaneously administering TRT/AAS. This is believed to be due to maintenance of intratesticular testosterone levels throughout treatment. One study examined the effects of exogenous testosterone on ITT levels and found that TRT resulted in a 94% decrease in ITT in otherwise healthy, reproductive aged men. However, after the addition of 250 IU of concomitant hCG, ITT levels only decreased by 7%. Furthermore, ITT levels increased by 26% in men who received 500 IU of concomitant hCG [83]. Hsieh and colleagues retrospectively reviewed 26 men who wished to preserve fertility while receiving coadministration of 500 IU hCG every other day and TRT. These researchers demonstrated that low dose hCG preserves all aspects of semen parameters after one year of follow-up and with no differences among types of TRT used [84]. While the data is limited, evidence suggests that hCG may be coadministered with TRT to preserve spermatogenesis.

6.2. Selective estrogen receptor modulators (SERMs)

SERMs are a class of medications that disrupt the binding of estrogen to the estrogen receptor within the hypothalamus through competitive antagonism. In men, estrogen is necessary for negative feedback inhibition of testosterone production and functions to downregulate GnRH and pituitary gonadotropin production. By blocking estrogen, SERMs increase GnRH release and subsequent gonadotropin production. This ultimately stimulates testicular function, spermatogenesis and increases ITT levels in men without causing hypogonadism [85]. Clomiphene citrate (CC) and tamoxifen are the most commonly used SERMs in the clinical setting. CC was popularized due to its stimulatory effect on ovulation in women while tamoxifen is known for its use in breast cancer. CC exists as a racemic mixture of enclomiphene (pure estrogen antagonist) and zuclomiphene (both estrogen agonist and antagonist). Zuclomiphene typically has a longer half-life (30 days) when compared to enclomiphene (10.5 hours) and may function as an estrogen agonist at high concentrations [86]. This variability in mechanism of action can lead to deleterious effects on male reproductive tissue. Fontenot and colleagues found that unopposed high doses of zuclomiphene in mice lead to severe testicular degeneration and arrested spermatogenesis [87]. This becomes important in patients who are on long-term CC, as the slower metabolism of this isomer may lead to higher concentrations of zuclomiphene over time. In fact, one study found zuclomiphene to be the predominant isomer in men after 6 weeks of CC therapy, with levels on average 20 times higher than enclomiphene. These reasons justify the need for the development of a pure selective estrogen receptor antagonist to minimize the potential undesirable side effects of zuclomiphene [88]. Unlike CC, tamoxifen is very active in peripheral tissue which allows for its success in treating hormone-sensitive breast cancer and early onset gynecomastia in men. Both CC and tamoxifen are known to increase gonadotropins and improve SA parameters in subfertile men [89].

CC is currently not FDA approved for the treatment of male infertility although it has been used off label for years in subpopulations of infertile men. Typical dosing consists of 25 to 50 mg administered oral and daily or every other day. Several studies have examined the use of CC in men with idiopathic oligozoospermia or azoospermia and have demonstrated favorable changes in semen analyses and hormone profiles following treatment [74,90,91]. While these studies are promising, there is minimal literature regarding CC use in males with TRT/AAS induced infertility, although several phase II/III trials show favorable results. One trial examined 12 men with secondary hypogonadism treated previously with TRT and found that oral enclomiphene increased testosterone and sperm counts when compared to topical testosterone [92]. An additional study examined 73 hypogonadal men with normal spermatogenesis who were randomized to 12.5 mg or 25 mg enclomiphene, topical TRT, or placebo. TRT was associated with increased rates of oligozoospermia and azoospermia and spermatogenesis was preserved in the enclomiphene groups [93]. Finally, a recent phase III, randomized, and double-blinded control trial by Kim and colleagues evaluated the effects of oral enclomiphene citrate and transdermal TRT on serum testosterone, LH, FSH and spermatogenesis. Serum testosterone was noted to increase in both treatment groups, but FSH, LH and spermatogenesis were only preserved in the enclomiphene citrate treatment group [85]. While this research is exciting and promising, there are

isolated reports of azoospermia possibly related to CC use and this must be discussed with patients prior to initiation of therapy. Pasqualotto and colleagues described a case report of three patients with severe oligozoospermia (<5 million/mL) who were later found to have azoospermia after treatment with CC [94]. While this level of evidence is very low and anecdotal, this case report highlights the potential risk of adverse effects which may be related to the variable agonist/antagonist effects of the zuclomiphene isomer within CC. Physicians should inform patients of the potential unpredictable results and obtain follow-up laboratory studies and semen analyses to ensure appropriate responses.

6.3. Aromatase inhibitors (AIs)

AIs are a class of medications that inhibit the enzyme aromatase which converts testosterone to estrogen within the testes, liver, brain, and adipose tissue. These medications are FDA approved for the treatment of early and late-stage breast cancer and commonly include anastrozole and letrozole. Since estrogen is an indirect mediator of testosterone production, AIs can be used off-label in men with infertility to increase gonadotropin production and stimulate spermatogenesis. This is of particular interest in obese men with large quantities of aromatase activity in peripheral adipose tissue and decreased testosterone-to-estrogen ratios. AIs can also be used to mitigate the side effects of hyperestrogenemia such as gynecomastia [19].

A recent meta-analysis by Del Giudice and colleagues examined the current literature and evidence regarding the use of AIs to treat male infertility. Three separate studies examined the effects of AIs on sperm concentration while five studies analyzed the effects of AIs on sperm motility. A meta-analysis was performed and revealed that AI therapy significantly increased sperm concentrations from the baseline and sperm motility. Most of these studies examined testolactone, anastrozole and letrozole and there appears to be no difference between AI therapy utilized [95]. While the number and quality of studies focusing on the use of AIs for male infertility remains low, the available data suggests that AIs may improve hormone and semen profiles in a safe and well-tolerated manner.

7. Clinical recommendations

Men with infertility related to AAS use may present in a variety of clinical scenarios that can be challenging for the clinician to navigate. For example, some may present with a remote history of AAS use while others may endorse concurrent AAS use. Several sources have outlined novel strategies regarding the management of AAS induced infertility and we attempt to summarize these below [19,77,89]. Regardless, the first and most important step in regaining fertility is the discontinuation of AAS use. If the patient is willing to wait and can tolerate the side effects of AAS cessation, conservative management is reasonable as spontaneous recovery will likely occur, although this can take 1–2 years. In those who desire a speedier recovery, 25 to 50 mg of daily CC should be started. As previously mentioned, a TRT taper can be offered to patients with severe hypogonadal side effects from AAS discontinuation. 3,000 IU of hCG every other day should also be started. This regimen should be maintained for at least 3 months before obtaining repeat SA and a hormonal panel. If estradiol remains elevated, consider adding anastrozole 1 mg twice weekly. If patients continue to exhibit persistent azoospermia and FSH remains undetectable, clinicians should discontinue CC and consider addition of 75 to 150 IU rFSH every other day. If this fails, testicular sperm extraction with possible microdissection should be considered. It is important to consider cryopreservation if oligozoospermia is encountered at any point during these treatments [77]. These management strategies are further outlined in Figure 3. Patients may also present with concurrent AAS use and desire preservation of fertility. In these cases, it is important to establish the patient's goals regarding the timing of desired pregnancy. For those who desire a pregnancy within 6 months, AAS cessation and initiation of the previously outlined regimen is recommended. If pregnancy is desired within 6 to 12 months, the patient may continue their AAS regimen plus the addition of 500 IU hCG every other day and CC 25 mg daily. If pregnancy is desired in over 12 months away, AAS use may be supplemented with 500 IU hCG every other day [89].

8. Future prevention

Despite the increasing prevalence of AAS use among men, there appears to be a lack of patient awareness regarding the harms with AAS use, especially the threat to male fertility. As previously mentioned, one study found that men who regretted AAS use were significantly more likely to have not comprehended the negative impact on future fertility [21]. Interventions and prevention strategies have long been recognized as a necessity to counteract the use of AAS. An excellent systematic review by Bates and colleagues analyzed 17 separate studies and 14 distinct interventions aimed at preventing misuse of drugs taken to enhance muscularity, performance, or appearance and may provide guidance for future prevention strategy [96]. Most of the interventions to date have focused predominantly on individual level factors within school environments, specifically concentrating on high school athletes, but the evidence outside of the sporting domain is severely lacking. These interventions were primarily educational and focused on factors such as ethics and values, harms, healthy alternatives, body image, and social norms. These same authors propose a socioecological approach to developing prevention strategies which recognizes the influence of individual characteristics and immediate social influences while also emphasizing the wider role of physical, social, and cultural factors. Future AAS prevention strategies that utilize a socioecological approach may be more effective at behavioral change and should be directed at multiple levels such as the individual, social network, institutional, community and societal levels [97].

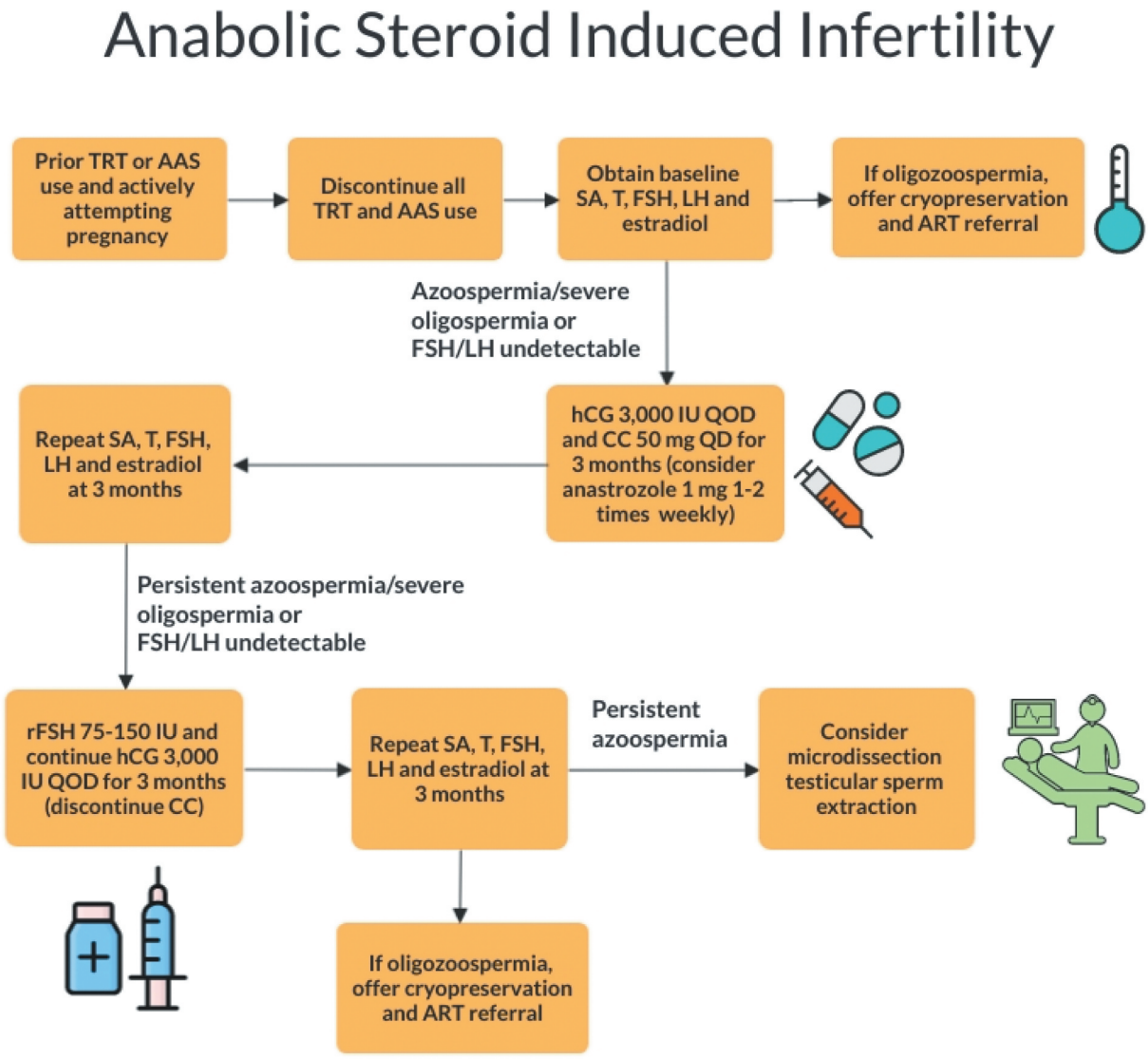

Figure 3. Management strategies for AAS induced infertility. TRT: testosterone replacement therapy, AAS: anabolic androgenic steroid, SA: semen analysis, T: testosterone, LH: luteinizing hormone, FSH: follicle-stimulating hormone, ART: assisted reproductive technology, hCG: human chorionic gonadotropin, QOD: every other day, CC: clomiphene citrate, QD: every day, rFSH: recombinant follicle stimulating hormone.

Since most AAS users are young adult men who are seeking to achieve an enhanced, muscular physique, local gyms, and fitness centers would be an ideal starting point to launch public awareness campaigns. Ideas could include providing information on maintaining a healthy lifestyle, supporting proper weight training technique, and promoting body positivity, as most men who are willing to try AAS have some level of body dissatisfaction. It may be beneficial to have prior AAS users openly share and discuss their experience with the consequences of AAS, particularly addressing addiction and behavioral changes associated with AAS use. Given the rise in social media usage amongst young adults, online social media platforms such as YouTube, Instagram, Facebook, TikTok, and bodybuilding forums would be key sites to target to raise awareness regarding the consequences of AAS use. To further increase health-care provider understanding of AAS and their consequences, it is crucial to continue publishing academic articles like this review. Each year, new anabolic and performance enhancing compounds are circulated globally and sold illegally. It is important for regulatory and governmental bodies to continue to criminalize and eliminate illegal manufacturing and distribution. Increased prevention campaigns from organizations such as the Food and Drug Administration, Drug Enforcement Administration, and World Anti-Doping Agency are crucial.

Another barrier to AAS prevention is the lack of precise diagnostic testing. Rahnema and colleagues accurately described the challenge that 'designer steroids' pose to regulatory bodies and anabolic steroid testing [98]. Typically, anabolic androgens from the 1960s which are not explicitly listed as controlled substances are chosen for repurposing. Chemists usually obtain bulk steroid precursors from foreign chemical suppliers and alter the compounds to improve bioavailability. Occasionally, chemists may employ methods to deliver potent androgens under the guise of pro-drugs that are unclassified compounds in the bottle

but are metabolized in vivo to scheduled AAS. Usually, a supplement company legally markets and distributes the product. After the FDA and anti-doping labs become aware of the product, analysis confirms the compound's identity. Once identified, and after an extensive legislative process and multiple costly bioassays, the compound is listed as a controlled substance and removed from the market. This process can take months to years. The lag time between introduction of a product and detection poses a significant challenge for AAS testing. Unfortunately, as quickly as substances are added to the controlled substance list, new compounds have emerged in the market to replace the previous generation.

9. Conclusions

As both the prevalence of AAS use and age of paternity continue to increase, clinicians are more likely than ever to encounter men with AAS induced infertility. It is important for physicians to understand this disease process and fully outline the risks associated with AAS use, including the effects on male reproductive health. Physicians must counsel patients in a healthy and non-judgmental fashion to discontinue AAS and offer a supplemental TRT taper for those with severe hypogonadal symptoms following AAS cessation. Although studies are limited, it appears that AAS induced infertility (prior or concurrent use) can be safely managed with the aforementioned regimen. CC and hCG appear to play crucial roles in the recovery of spermatogenesis. Despite increased interest and research examining AAS use, it appears that studies outlining successful AAS prevention tactics are lacking. Further research examining the effectiveness of socioecological-based AAS prevention strategies may be of particular interest.

10. Expert opinion

Anabolic steroid use is on the rise and users continue to exhibit lack of understanding regarding the potential effects on male fertility. In addition, it appears that SARMs are becoming increasingly popular among men and can have similar adverse effects on male fertility and testosterone production. The available literature, although limited, suggests that spermatogenesis can be safely recovered using a combination of SERMs, hCG, AIs and rFSH, although additional studies are needed to further establish these findings. The lack of clinical evidence regarding the management of AAS induced infertility is a large barrier to implementation of the aforementioned regimens into clinical practice. The large majority of AAS use is illicit and banned in most countries. AAS users infrequently seek care from medical providers due to the perceived lack of knowledge regarding AAS use and physician distrust in addition to fears of discrimination. In fact, most of these men self-regulate their usage and tend to be relatively disciplined and precise. Physicians may not come in contact with AAS users until problems arise, which may be years after their first usage and once dependence has set in. The variability and number of anabolic steroids used are also barriers to further research. There are over 20 different types of common anabolic compounds utilized by AAS users. These substances have varying levels of potency and differing mechanisms of action. AAS users will often combine multiple compounds at variable dosages which can pose a challenge to researchers. These obstacles, in addition to the shroud of secrecy surrounding AAS use, makes it difficult to conduct extensive, large-scale clinical studies which will be a necessity over the next five to ten years.

More importantly, despite increased interest and research in the field of AAS over the last few decades, there appears to be a lack of evidence regarding effective prevention tactics. While anabolic steroid prevention strategies have largely been focused on the individual level, further investigation is necessary and should be approached in a socioecological manner, targeting not just individuals but multiple ecological levels including social network, institutional, community and societal. The lack of regulation and quality control regarding illegal AAS manufacturing is another barrier to studying AAS prevention. Furthermore, it is difficult to launch prevention campaigns as there is no single product to target and no central organization that has interest to increase public awareness unlike other substance abuse prevention campaigns (opioid epidemic, pharmaceutical companies and the Food and Drug Administration). Increased FDA and governmental regulation of illegal AAS manufacturers will be necessary to prevent future AAS use, especially as AAS use is likely to worsen with the aging population and the increasingly hypercompetitive nature of sports. Continued prevention strategies from athletic organizations such as the World Anti-Doping Agency will also be crucial. It is prudent to continue to publish articles such as these to increase physician awareness regarding AAS and their consequences. Finally, it appears that a large proportion of young adult men obtain most of their AAS information via online social media platforms such as Facebook, YouTube, Instagram, TikTok, and online bodybuilding forums. As social media use increases and platforms continue to rapidly evolve, it will be prudent to examine prevention strategies targeting the different realms of the social network in the coming years.

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