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REVIEW ARTICLE

Recovery of spermatogenesis after androgenic anabolic steroids abuse in men. A systematic review of the literature*

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Abstract
Objective: This systematic review aims to evaluate the optimal treatment for male infertility resulting from Anabolic Androgenic Steroids (AAS) abuse.
Methods: A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies that compared different protocols for the recovery of spermatogenesis in patients after AAS use were included.
Results: 13 studies investigating different protocols to restore spermatogenesis in patients with AAS abuse met the inclusion criteria. The available agents that showed restoration of spermatogenesis include injectable gonadotropins, selective estrogen receptor modulators, and aromatase inhibitors, but their use is still poorly described in the literature.
Conclusions: Clinicians need to be aware of the detrimental effects of AAS on spermatogenesis. AAS-associated infertility may be reversible, but sperm production may take over a year to normalize. Both conservative and aggressive treatment can boost spermatogenesis with positive results. Further understanding of male reproductive endocrinology and high-quality data on the field of restoration of spermatogenesis after AAS abuse are warranted.

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PALABRAS CLAVE
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Citrato de clomifeno;
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Infertilidad masculina;
Espermatogénesis;
Testosterona

Recuperación de la espermatogénesis tras el abuso de esteroides anabólicos androgénicos en varones. Revisión sistemática de la literatura

Resumen

Objetivo: El objetivo de esta revisión sistemática es identificar el tratamiento óptimo para la infertilidad masculina derivada del abuso de esteroides anabólicos androgénicos (EAA).

Métodos: Se llevó a cabo una revisión sistemática según la declaración Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Se incluyeron estudios que comparaban distintos protocolos para la recuperación de la espermatogénesis tras el uso de EAA.

Resultados: Un total de 13 estudios que investigaban diferentes protocolos para recuperar la espermatogénesis en pacientes con abuso de EAA cumplieron los criterios de inclusión. Entre los agentes disponibles que demostraron eficacia en la recuperación de la espermatogénesis se encuentran las gonadotropinas inyectables, los moduladores selectivos de los receptores de estrógenos y los inhibidores de la aromatasa (AI), pero su uso apenas ha sido descrito en la literatura.

Conclusiones: Los médicos deben conocer los efectos adversos que los EAA pueden tener sobre la espermatogénesis. La infertilidad asociada a los EAA puede ser de carácter reversible, pero la producción de espermatozoides puede tardar más de un año en normalizarse. Tanto el tratamiento conservador como el agresivo pueden estimular la espermatogénesis con resultados satisfactorios. Se requiere una mayor comprensión de la endocrinología reproductiva masculina y datos de alta calidad sobre la recuperación de la espermatogénesis tras el abuso de EAA.

Introduction

The development and synthesis of Anabolic Androgenic Steroids (AAS) were obtained by the anabolic property of testosterone (T). AAS have longer half-lives, higher potency action, and fewer liver side effects compared to T. These ''Appearance and performance-enhancing drugs'' gained popularity due to their impact on muscle mass in athletes.[1] However, the World Anti-Doping Agency (WADA) banned users for both their performance-enhancing effects and negative, dangerous impacts.[2] In 2010 the national anti-doping agencies published a ''Strategy to Stop Steroid Use'' which estimated that global prevalence was higher in men (6.4%) than women (1.6%).[3]

Testosterone is primarily responsible for male secondary puberty traits, sperm maturation and libido initiation,[4] but there are varying opinions on what constitutes normal plasma levels, depending on age and measurement methods used.[5] The activation of specific receptor sites is mediated by downstream processes essential for growth and development.[6] The Leydig cell's mitochondria synthesize testosterone from cholesterol, which then converts into C-19 testosterone[4] within the endoplasmic reticulum, and then released into the circulation.[4] At the periphery, it binds to target cells, acting as a prohormone and produce anabolic or androgenic effects, through conversion to a more potent compound, 17-α-dihydrotestosterone.[6] Daily T production rates vary among different races (Caucasian: 9.11 ± 1.11 mg/day; Asians producing 7.22 ± 1.15 mg/day.[7]

The majority of testosterone circulates in the bloodstream bound to either albumin or sex hormone-binding globulin (SHBG), with only a small percentage remaining as free testosterone that binds to tissue receptors.[8] Metabolism occurs through three pathways: a) aromatization by CYP19 into estradiol, b) conversion into dihydrotestosterone via a reductase enzyme and c) elimination from the liver through the kidney.[8]

The hypothalamus regulates T production via GnRH, which triggers the secretion of LH and FSH by target cells in the anterior pituitary gland. LH acts on Leydig cells, while FSH activates testicular Sertoli cells for spermatogenesis and increases aromatase activity.[9] Other peptides such as insulin-like growth factors, leptin, ghrelin, and TNF-B also play a role in controlling T production.[10] Testosterone's anabolic properties boost lean body mass, muscle size, strength, athletic performance, and aerobic capacity.[11]

AAS are obtained by modifying the molecule structure to increase activity. They have a C17 polycyclic core with three cyclohexanes fused together alongside one cyclopentane ring.[6] The anabolic effects are dose-dependent and mostly at higher physiological levels,[11] mainly observed through use by amateur athletes for cosmetic reasons.[12] Safety risks are higher because it is frequently obtained from black markets or contaminated dietary supplements (15–22%).[11,12]

Testosterone therapy is primarily used to treat hypogonadism, and controversially employed for conditions such as low libido, erectile dysfunction, exhaustion/depression and lack of attention. Despite being scientifically unproven, some patients/users have claimed these benefits.[11,12]

Unwanted effects such as acne, alopecia, urinary tract problems, erectile dysfunction, libido loss, hypogonadotropic hypogonadism, infertility, gynaecomastia, hepatic neoplasms and jaundice may occur and are related to the dose and treatment length.[13] Increase in conjugated bilirubin, AST, serum creatinine, BUN, uric acid, and ALT. Additionally, hypertension, arrhythmia, erythrocytosis, ventricular dysfunction, systemic allergies, thrombosis, and kidney damage, are related to long-term AAS use.[13,14] Other harmful known effects are, secondary rhabdomyolysis, myocardial infarction, sudden death, and diffuse proliferative membrane glomerulonephritis compared with non-users with a 4.6-fold greater mortality.[15] Erectile dysfunction (ED) may be the first sign of prolonged AAS users, probably due to high estrogen or low DHT.[16]

AAS abuse may cause 2% of male infertility[16] by blocking the hypothalamic-pituitary axis, lowering FSH, LH and intratesticular testosterone (ITT) and a spermatogenesis impairment.[13,17] The release of GnRH and LH from the hypothalamus and pituitary is directly suppressed, lowering endogenous testosterone release into the downstream that leads to testicular tubular atrophy.[17] Infertil-

ity in such cases is frequently reversible, but it may take over a year to recover sperm production.[18]

The management of low sperm production, with a resulting diminished seminal sperm concentration or azoospermia after abuse, poses a challenge for couples with limited time due to advanced female age.[18] Treatments that effectively reduce waiting time and increase success rates are lacking.

This systematic review aims to determine the optimal treatment for male infertility resulting from testosterone and AAS abuse.

Methods

This systematic review has been developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis recommendations: the PRISMA statement.[19]

Search strategy

A systematic search was conducted including PubMed, Cochrane, and Scopus from 1980 to November 2022. Studies that compared different protocols for the recovery of spermatogenesis in patients after AAS use were included. Reference lists of relevant articles were also searched for any additional studies not covered by the literature search. The search combined terms and descriptors related to the variants of the interventions, the study population, and the results: anabolic androgenic steroids, testosterone, infertility, azoospermia, oligozoospermia. The strategy was modified to adjust to the syntax used in each database consulted.

All the articles retrieved from the search in the first selection were evaluated independently by two researchers (JM and OR). The full texts that met the inclusion criteria were then examined. Both authors assessed the quality and eligibility of the extracted data, solving discrepancies by agreement.

Eligibility criteria

Clinical trials, cohort studies, and studies that have clearly identified and individualized AAS abuse cases were included in this study. The study subjects were men with a history of AAS abuse and presented clinical symptoms and/or laboratory tests compatible with a hypogonadism diagnosis. Further details about study eligibility criteria and included or excluded studies are shown in the PRISMA flowchart diagram (Fig. 1).

Risk of bias assessment

Study quality was assessed by two reviewers (JM and OR), in the Newcastle-Ottawa Scales (NOS) guidelines for measuring the quality of included studies.[20] We performed an assessment of bias in the studies regarding the selection process, comparability of cohorts, and the determination of the results.

Outcome measures

The primary outcome measure was the effectiveness in restoring spermatogenesis for the different treatment protocols. Other variables to be evaluated were the time intervals necessary for the restoration of spermatogenesis or recovery from hypogonadism.

Results

The search returned a total of 313 records, but 286 were excluded after examining the titles and abstracts of these manuscripts. Of the remaining 27 studies that were deemed eligible by one or both reviewers, only 13 were included in the review.[21–33] Fig. 1 describes the study selection process in detail.

Description of included studies

13 studies investigating different protocols to restore spermatogenesis in patients with AAS abuse met the inclusion criteria.[21–33] Details of the included studies are summarized in Table 1. All studies with NOS scores > 7 were considered to be of high quality.

The effect of gonadotropins, SERMs, and AIs after AAS abuse on the recovery of spermatogenesis and reproductive outcomes is described in Tables 2–4.

Discussion

Main findings and clinical considerations

ITT concentration is crucial for spermatogenesis, and addressing hypogonadism is key to managing AAS-induced male infertility.[16] After cessation of AAS use, symptomatic hypogonadism may develop, but can slowly recover within 4–30 months,[18,34] with some individuals requiring endocrine and reproductive function restoration through treatment. Selective estrogen receptor modulators (SERMs) such as tamoxifen and CC have been studied for their potential in increasing ITT levels by blocking negative estrogen feedback through competitive antagonism that increases GnRH/gonadotropin production in men without primary hypogonadism.[16] Clinically effective doses of CC are reported at alternate day dosages of 25 mg to manage low testosterone levels

Our systematic review identified SERMs, aromatase inhibitors (AIs), and gonadotropin analogs as potential treatments for AAS-induced hypogonadism (see Tables 3 and 4).

Specifically, SERMs act by blocking negative estrogen feedback through competitive antagonism. This leads to increased GnRH and gonadotropin production in men without primary hypogonadism.[34] Clinically, tamoxifen and clomiphene citrate (CC) are two of the most used SERMs. CC is a racemic mixture of shorter-acting enclomiphene (purely anti-estrogenic) and longer-acting zuclomiphene (both estrogen agonist and antagonist) having a serum half-life of 5 days.[35]

Since 1966, the off-label CC use in males has demonstrated improvements in serum testosterone levels and hypogonadal symptoms, indicating its HPG axis-boosting actions. CC 25 mg on alternate days has been successfully used for the management of low testosterone.[36,37]

Aromatase inhibitors (AIs) like anastrozole and letrozole are utilized in breast cancer treatment. They hinder the aromatase enzyme's action of converting testosterone to estrogen, leading to decreased estrogen levels. The off-label use of AIs boosts FSH production, strengthens GnRH pulses, and ultimately enhances spermatogenesis in men.[38]

Letrozole (2.5 mg daily), improves the T/E ratio and sperm parameters, with up to 20% spontaneous pregnancy rate for oligospermic men and 24% return of sperm to the ejaculate for previously azoospermic men.[38] There is a lack of prospective trials assessing the use of AIs in infertile men with prior testosterone analogs and/or AAS abuse. The treatment of clomiphene and AIs concurrently has not been studied, but based on their respective rationality, it may be justifiable to combine them for patients exhibiting abnormal testosterone level and T/E ratios.[38]

Human Chorionic gonadotropin (hCG) and FSH are employed to stimulate testosterone production and restore spermatogenesis in AAS-abusers. hCG has a longer circulating half-life than endogenous LH, and increased receptor activity due to its unique β-subunit that is virtually identical to the LH β-subunit, and is the only on-label drug for treating male infertility. Recombinant hCG from a urinary

Table 1 Description of articles included.

Study ID	Area/duration	Design of the study	Number of participants	Age	Population	Outcomes considered	Quality of studies
Liu et al.[21] 2009	Australia 1981–2008	Prospective, nonrandomized (two centers)	75	34 ± 1	Idiopathic hypoandrogenic: 34 (45.3), Kallmann: 17 (22.7), Pituitary: 24 (32)	Semen parameters, testis volume, clinical pregnancies	8/9
Wenker et al.[22] 2015	USA 2006–2013	Retrospective cohort study (two centers)	49	40.5 (21–63)	45 (91.8) Azoospermia, 4 (8.2) Severe oligospermia	Hormone values, semen parameters and clinical pregnancies	7/9
Kohn et al.[23] 2016	USA 2004–2015	Retrospective cohort study (single center)	66	40.2 ± 8.7	54 (81.8) Azoospermic, 12 (18.2) Cryptozoospermia	Hormone values and semen parameters	7/9
Andrabi et al.[24] 2021	India 2014–2019	Prospective, nonrandomized (single center)	56	Responders 32.00 ± 4.31 No responders 30.40 ± 3.27	Idiopathic severe oligozoospermia	Hormone values and semen parameters	8/9
Lima et al.[25] 2021	USA 2018–2020	Prospective, nonrandomized (single center)	Total: 31 Clomiphene citrate (n = 21) Clomiphene citrate + hCG (n = 10)	39.6 ± 6.6	Infertile men with secondary hypogonadism and testosterone abuse	Hormone values and semen parameters	8/9
Whitten et al.[26] 2006	USA 2000–2005	Retrospective cohort study (two centers)	10	29.3 ± 5.9	Idiopathic hypoandrogenic: 4 (40), Kallmann: 4 (40), Panhypopituitarism: 2 (20)	Hormone values, semen parameters and clinical pregnancies	7/9

Table 1 (*Continued*)

Study ID	Area/duration	Design of the study	Number of participants	Age	Population	Outcomes considered	Quality of studies
Kaminetsky et al.[27] 2013	USA 2012	Prospective, randomized, open-label (two centers)	Total: 12 Enclomiphene citrate (n = 8) Topical testosterone (n = 4)	46 (41–59)	Men with secondary hypogonadism treated previously with topical testosterone	Hormone values and semen parameters	Unclear risk of bias
Wiehle et al.[28] 2014	USA 2011	Prospective, randomized, double-blind (multiple center)	Total: 121 Enclomiphene citrate 12.5 mg (n = 27) Enclomiphene citrate 25 mg (n = 33) Topical testosterone (n = 33) Placebo (n = 28)	49.7 ± 11.58 49.2 ± 10.94 52 ± 10.58 51.6 ± 11.57	Men with secondary hypogonadism	Hormone values and semen parameters	Low risk of bias
Helo et al.[29] 2015	USA 2015	Prospective, randomized, double-blind (single center)	Total: 26 Clomiphene citrate (n = 13) Anastrozole (n = 13)	35 ± 6.5 33 ± 3.9	Idiopathic hypoandrogenic	Hormone values	Unclear risk of bias

Table 1 (*Continued*)

Study ID	Area/duration	Design of the study	Number of participants	Age	Population	Outcomes considered	Quality of studies
Kim et al.[30] 2016	USA 2016	Two prospective, randomized, double-blind (multiple center) studies: ZA304 and ZA305	Total: 256 Enclomiphene citrate 12.5 mg (n = 43) Enclomiphene citrate 25 mg (n = 42) Topical testosterone (n = 85) Placebo (n = 86)	Study ZA304 EN: 49.1 ± 7.4 TT: 47.4 ± 7.2 Placebo 47.2 ± 9 Study ZA305 EN: 47.3 ± 8.8 TT: 45 ± 8.2 Placebo 47.5 ± 8.9	Men with secondary hypogonadism	Hormone values and semen parameters	Low risk of bias
Saylam et al.[31] 2011	Turkey 2006–2009	Prospective, nonrandomized (single center)	27	34.92 ± 6.66	Idiopathic hypoandrogenic	Hormone values, semen parameters, testis volume	7/9
Gregoriou et al.[32] 2012	Greece 2008–2011	Prospective, nonrandomized study (single center)	Total: 29 Letrozole (n = 15) Anastrozole (n = 14)	NR	Idiopathic hypoandrogenic	Hormone values, semen parameters, testis volume	8/9
Shoshany et al.[33] 2017	Turkey 2010–2016	Retrospective survey	86	37 (32–41)	Idiopathic hypoandrogenic: 71 (82.5), cryptorchidism: 11 (12.7), varicocele repair: 4 (4.6)	Hormone values and semen parameters	7/9

NR: not registered; EN: enclomiphene citrate; TT: topical testosterone.

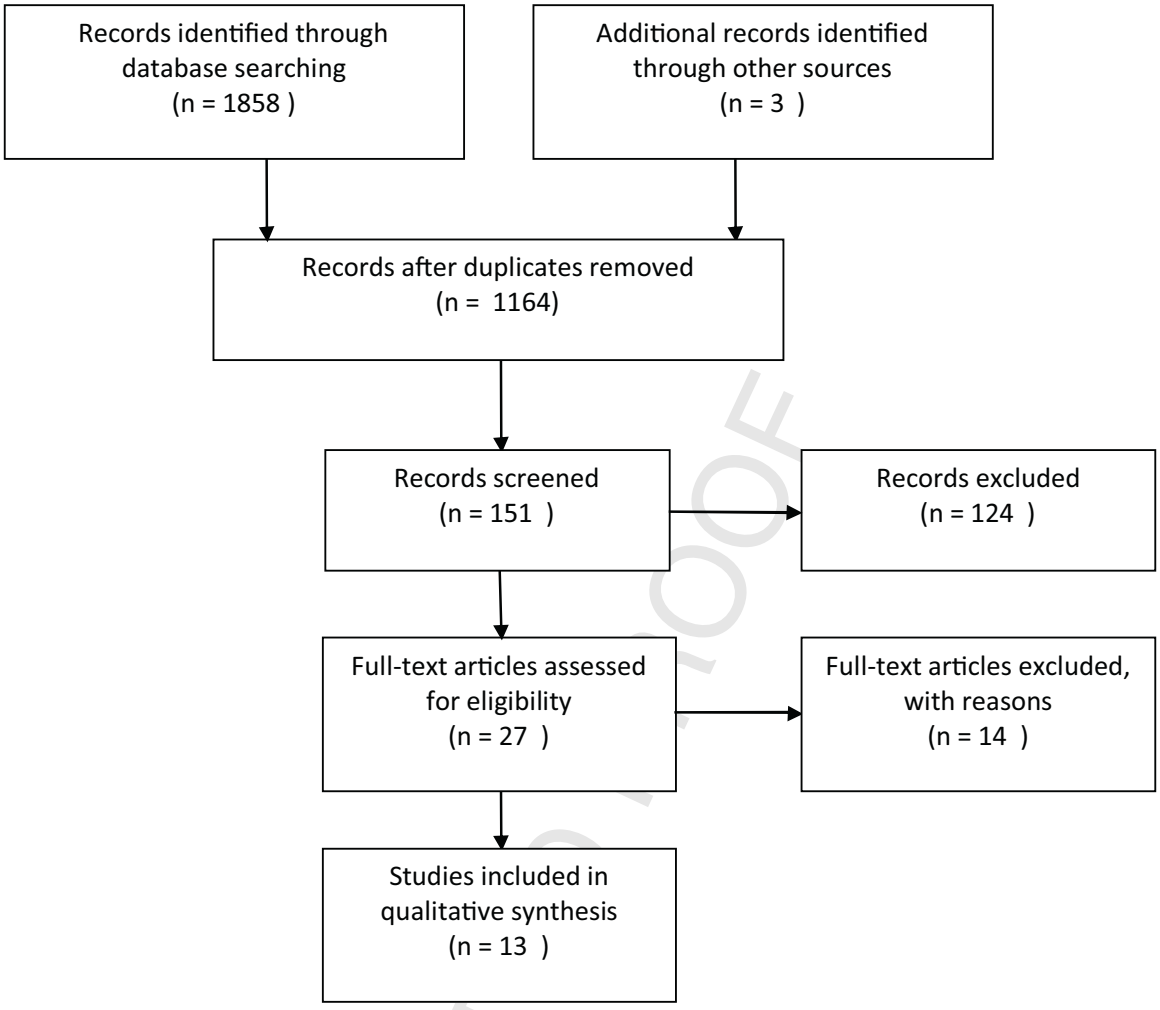

Figure 1 Preferred Outcome Items for Systematic Reviews and Meta-analysis flow diagram detailing selection of studies for inclusion.

Table 2 Gonadotropins for recovery of spermatogenesis.

Author	hCG dose (IU)	Dose frequency (per week)	Number of patients (n)	Suplement	Duration (months)	Spermatogenesis recovery (%)	Pregnancy rate (%)
Liu et al.[21] 2009	1500–2000	2–3	75	FSH	3–6	90	50.6
Wenker et al.[22] 2015	3000	3	49	FSH, CC, anastrazole	14	95.9	38.8
Kohn et al.[23] 2016	3000	3	66	CC	12	69.7	NR
Andrabi et al.[24] 2021	6500	1	56		3–6	83.9	NR
Lima et al.[25] 2021	2000	3	10	CC	3–5	60	NR

CC: clomiphene citrate; NR: not registered.

source with equivalent activity is available, as well as recombinant FSH (rFSH) with higher specificity for the FSH receptor.[37] Gonadotropin analogs can be administered assuming they are safe and effective in treating hypogonadal symptoms, hastening recovery time, and avoiding the risks associated with Creutzfeld–Jakob disease, becoming an alternative pharmacologic treatment option for men. The usual treatment regimen starts with hCG only doses of 1500 to 5000 IU 2–3 times per week, for three to six months and then adding recombinant FSH in doses of 75–400 IUs 2–3 times per week in men who did not regain spermatogenesis on hCG alone.[37]

Table 3 Clomiphene citrate and enclomiphene citrate for recovery of spermatogenesis.

Author	Dose per day	Number of patients (n)	Duration (months)	Spermatogenesis recovery (%)	Pregnancy rate (%)
Whitten et al.[26] 2006	50 (CC)	4	3 weeks	100	75
Kaminetsky et al.[27] 2013	25 (EN)	8	3–6	100	NR
Wiehle et al.[28] 2014	12.5 - 25 (EN)	56	3	94.2	NR
Helo et al.[29] 2015	25 (CC)	13			7.6
Kim et al.[30] 2016	12.5 - 25 (EN)	85	4	100	NR

CC: clomiphene citrate; EN: enclomiphene citrate; NR: not registered.

Table 4 Aromatase inhibitors: letrozole and anastrozole for recovery of spermatogenesis.

Author	Dose per day	Number of patients (n)	Duration (months)	Spermatogenesis recovery (%)	Pregnancy rate (%)
Saylam et al.[31] 2011	2.5 (L)	27	6	51.8	NR
Gregoriou et al.[32] 2012	2.5 (l) o 1 (az)	15 (l) 14 (az)	6	73.4 (l) 78.6 (az)	NR
Helo et al.[29] 2015	1 (az)	13	3		23
Shoshany et al.[33] 2017	1 (az)	21	4	85.7	NR

L: letrozole; Az: anastrazole; NR: not registered.

As a general rule, men seeking conception should avoid TRT/AAS, and if they are taking such agents, they must be discontinued immediately. Following this, the recovery of spermatogenesis may be a slow process, particularly for those with previously poor baseline testicular function, a long history of treatment, or older age at cessation.[37]

A proposed protocol includes discontinuing the pharmacy abuse and determining baseline seminal analysis and hormone levels (FSH, LH, T), remembering that endogenous levels might be low. It is critical to consider cryopreservation whenever a patient's sperm count improves and becomes oligozoospermic.

Therapy should begin 50 mg PO clomiphene citrate every other day for 3 months and since then add 2000 IU of hCG every other day. Semen Analysis and hormones should be repeated after 3 months. If the estradiol level is very high, anastrozole 1 mg PO twice-weekly might be administered. FSH 75 IU every other day should be added if azoospermia or severe oligospermia continues. If the next seminal analysis is three months later and still exhibits persistent azoospermia, testicular sperm extraction (TESE)/micro should be explored.[39]

Regarding the management of sexual dysfunction in AAS abuse, the correction of the underlying hormone imbalance should be the first approach.

Strengths and limitations

This study provides valuable insights into strategies to restore spermatogenesis after AAS abuse. While it is one of the few systematic reviews on the subject, there are some limitations that should be taken into account when interpreting its findings. These include the incorporation of studies with patients suffering from hypogonadism not exclusively due to AAS, and also the limited sample sizes in many observational studies. Furthermore, inconsistencies in treatment regimens and follow-up periods prevent a meta-analysis from being carried out. Lastly, pregnancy outcomes were not available for most studies, which hindered our ability to evaluate fertility outcomes fully.

Future directions

Physicians must be aware of the increasing number of men seeking treatment for infertility related to prior AAS use.[37] Given the rising average paternal age and growing use among young to middle-aged men, it is essential that specialists conduct a detailed history to gather information on potential fertility side effects. Additionally, a recent survey revealed that an alarming 25% of clinicians used exogenous testosterone as empiric treatment for idiopathic male infertility.[40] With emerging evidence supporting restorative therapies in recovering spermatogenesis within this population, knowledge regarding various treatment options and their impact on HPG axis function is crucial. Understanding the clinical uses and effectiveness of CC and other SERMs can aid in the implementation of newer agents, even if they are off-label treatments.

Polydrug use, common among athletes and sometimes prescribed by doctors, involves combining AAS with other substances like hCG. It's crucial to understand the various treatment options for restoring spermatogenesis in this population and their effects on the HPG axis. While studies focusing on pharmacologic strategies for male testicular dysfunction secondary to AAS are limited, our meta-analysis shows that SERMs, AIs, and gonadotropins improve hormone and semen profiles safely. However, more randomized multicenter trials are necessary to determine whether HCG ± rFSH or SERMs can effectively stimulate spermatogenesis recovery in this setting.

Conclusions

AAS use affects male reproductive health, as observed by andrology specialists. Male infertility is probably an under-diagnosed treatable form of drug-related infertility. There is evidence that suggests that AAS-associated infertility is reversible, but it may take over a year for sperm production to return to normal levels. Conservative management and treatment should be considered to improve spermatogenesis. However, aggressive treatment with exogenous gonadotropins is also reported to have positive outcomes.

Potentially negative, serious long-term effects on the reproductive system and general health of AAS users warrant further actions to manage this global public health issue, together with education of the general population, athletes, and healthcare providers.

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