Systematic Review

Use of Anabolic-Androgenic Steroids and Male Fertility: A Systematic Review and Meta-analysis

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Abstract

Background: Anabolic-androgenic steroids (AASs) are often used by men for bodybuilding and to improve sports performance. The use is not limited to professional competitive athletes, but many amateur men. **Objective:** The objective of this study was to assess and systematically review the effects of AAS on male fertility parameters, spermiogram, testosterone, follicle-stimulating hormone (FSH) and luteinising hormone (LH) and to review reversibility and other morbidity impacting fertility. **Methods:** Eligibility criteria - We included studies mentioning data about adult males using supraphysiologic doses of AAS for sports performance or appearance enhancement, with comparison data from general population or matched controls if available reporting fertility parameters and sexual performance. Information sources - A systematic literature search was performed using PubMed, MEDLINE, EMBASE, Google Scholar and World of Science. Controlled clinical trials randomised or nonrandomised (if available), case series with or without matched controls, case reports, cross-sectional surveys, reports on follow-up of subjects caught in doping test and their fertility parameters when reported. Risk of bias/quality assessment - The quality assessment of the included studies was performed using the Newcastle–Ottawa Scale. **Results:** Included studies - Thirty-two studies were included. There were 12 cohort studies, 5 case–control studies, 9 cross-sectional surveys and 6 case reports. The study population comprised 9371 individuals, of which 2671 were AAS users. Synthesis of results - AAS users had reduced levels of FSH and LH than the naïve population. These levels remained low for 3–6 months after stopping AAS. One year after stopping AAS, the users and naïve population had insignificant differences in FSH and LH values. The total testosterone (TT) levels were comparable in users and naïve populations at baseline, 3 months and 6 months after stopping, but at 1 year, TT values were lower in AAS users. Sperm concentration in AAS users and naïve population was similar, but sperm motility was lower in AAS users. The testicular size was lower in AAS users. The erectile function improved with AAS use, but on withdrawal, there was decreased libido and erectile dysfunction. Most AAS users need additional medications to mitigate detrimental effects on fertility. Description of the effect - AAS use negatively impacted the gonadotrophin levels and had

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lower sperm motility and testicular size. Strength - Comprehensive review of 32 publications, study population of 9371 individuals, of which 2671 were AAS users, meta-analysis of reproductive hormones, semen parameters and testis size. **Limitations:** The limitations are small sample size of most of the studies, polypharmacy, lack of information on dosing and high heterogeneity. **Interpretation:** AAS use is detrimental for sperm motility and has a partially reversible negative impact on male fertility. Users must be cautioned about its negative impact on libido and erectile function.

Registration: PROSPERO Registration No. CRD42023411294.

Keywords: *Androgen abuse, androgenic anabolic steroids, bodybuilding, doping in sports, erectile dysfunction, infertility, spermatogenesis*

Introduction

Anabolic-androgenic steroids (AASs) and performance-enhancing drugs (PEDs) represent a myriad of substances used to enhance one's physique and/or improve physical performance. These include but are not limited to testosterone esters, synthetic androgens, aromatase inhibitors (AIs), selective estrogen receptor modulators (SERMs), selective androgen receptor modulators (SARMs), human growth hormone (hGH) and fat-burning compounds. An estimated 2.9–4 million young male Americans abuse AAS in their lifetime and is a reflection of the pertinent and prevalent global medical issue.[1] The Bay Area Laboratory Co-operative scandal[2] changed the face of doping in USA. In this scandal an Illinois chemist Patrick Arnold distributed PED via personal trainer Greg Anderson to high performance athletes between 1988-2002. These were seemingly undetectable in routine drug testing. This initiated the era of the infamous "sport doping". The sport doping is now a serious offence for professional, athletes.[3] However, unregulated rampant misuse has created a medical menace due to its multiple physiological and psychiatric deleterious effects.[4] Of these PEDs, AAS is misused by professional athletes and by common men for personal physical enhancement. Recent estimates report that 4%–12% of US high school boys have used AAS at some time in their lives.[5] The users of AAS may at first glance appear genetically superior but have a higher probability of being unfit for reproduction. Famously coined as the Mossman and Pacey paradox,[6] whereby abusers consume these to enhance their physical features to attract a partner despite being aware of the reproductive side effects. This 'fertility fitness paradox' is exposed subsequently by often irreversible body dysmorphic disorders.[7] The desire amongst competitive athletes to succeed is a powerful stimulus and using legal substances for illegal purposes to obtain these goals has become an increasingly large concern. The long-term effects of AAS use on the body are still not fully understood and may include liver damage, heart disease, infertility and psychiatric effects such as depression, aggression and psychosis. A clinician's warnings will only gain credibility if they have a sound understanding of the issues related to AAS use so that they can have an informed conversation with the patient or user.

Previously published meta-analysis[8] on this issue included fewer studies with <100 subjects. It did not include the comparison between AAS users and non-users. Moreover, the review also included studies with women subjects.[8] Another systematic review and meta-analysis included fewer subjects and also focused on metabolic parameters in addition to reproductive and sexual parameters.[9] Moreover, some recently published work on this issue did not perform meta-analyses.[10,11] The purpose of the present meta-analysis and systematic review is to determine the effects of AAS on male fertility amongst AAS abusers compared with non-abusers. We also aim to discuss the recent available evidence on the effects of long-term use of AASs.

Materials and Methods

Aim of the review

The present study aims to systematically review the effects of AAS on male fertility. The main outcome is to evaluate the effects on male fertility parameters: spermiogram, testosterone, FSH and LH. The secondary outcome parameters were to look at the reversibility of these effects, and other morbidities such as testicular size and erectile function which impact fertility.

Literature search

This review was performed according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. An extensive literature search was performed in March 2023, using PubMed, MEDLINE, EMBASE, Google Scholar and World of Science. Medical Subject Heading (MeSH) terms and keywords such as 'anabolic androgenic steroids,' 'male fertility,' 'testosterone congeners' and 'doping' were used. The search was restricted to English literature. The search was restricted to studies published between 1 January 2000 and 31 December 2022. Studies before 2000 were not considered the World Anti-Doping

Agency (WADA) came into existence in 1999. Many criteria were laid down and definitions were formulated. Animal studies and studies on women were also excluded. PROSPERO database was searched to see if any such review existed, and subsequently, the review protocol was registered and published in PROSPERO vide registration No. CRD42023411294.

Selection criteria

The Patient Intervention Comparison Outcome Study type (PICOS) model was used to frame and answer the research question.

- Population: Adult males using AAS for sports performance or appearance enhancement
- Intervention: Supraphysiologic doses of AAS
- Comparison: General population or matched controls if available. As clinical trials with AAS are ethically not possible, studies without control groups were also included
- Outcome: Fertility parameters and sexual performance
- Studies: Controlled clinical trials randomised or non-randomised (if available), case series with or without matched controls, case reports, cross-sectional surveys, reports on follow-up of subjects caught in doping test and their fertility parameters when reported.

Study screening and selection

Two independent authors screened all retrieved records through Covidence Systematic Review Management® (Veritas Health Innovation, Melbourne, Australia). A third author solved discrepancies. Studies were included based on PICOS eligibility criteria. Retrospective, prospective non-randomised and randomised studies were accepted. Meeting abstracts and case reports were also included. Reviews, letters to the editor and editorials were excluded. The full text of the screened articles was selected if found relevant to the purpose of this study. Cross references of included studies were also screened for eligibility.

Statistical analysis

Data on reproductive hormones, follicle-stimulating hormone (FSH), luteinising hormone (LH), total testosterone (TT), semen parameters and testis size were analysed using the inverse variance of the standardised mean difference (SMD) with a random effect, 95% confidence intervals (CI) and *P* values. Significance was set at $P < 0.05$ and a 95% CI. Study heterogeneity was assessed utilising the I^2 value. Substantial heterogeneity was defined as an $I^2 > 50\%$. Meta-analysis was performed using Review Manager (RevMan) 5.4 software by Cochrane Collaboration, UK. Parameters such as FSH, luteinising hormone (LH), TT, semen parameters and testis size were considered for meta-analysis. AAS compounds used and the pattern of use of other agents was disregarded. The assay method for hormone analysis was disregarded. For studies reporting hormone values in international units, the values were converted to conventional units using online tools from UnitsLab.[12] Missing data in the full-text articles were asked for from the authors. When studies reported median and range or confidence interval, the median was considered mean and standard deviation was calculated from online tools or RevMan calculator. For analysis at the beginning of the follow-up, AAS users were compared with the naïve population. At 3- and 6-month baseline, values at stopping AAS use and follow-up values were compared. At 1 year after stopping AAS, the AAS group was compared with the naïve population from the same study. Meta-analysis was performed if two or more studies or datasets reported data from the study and comparison group. The remaining results were summarised in systematic review.

Risk of bias/quality assessment

Risk of bias (ROB1, ROB2 or ROBINS-I) was not used as no randomised interventional or non-randomised trials with the intervention were available. Such trials are not ethically possible with AAS. The quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS).[13] Two authors (PMM and GRT) analysed the studies for quality assessment consensually. The quality assessment of studies as per the NOS scale was done separately for case–control and cohort studies under the subheadings of selection, comparability and exposure as outlined in the NOS coding manual.

Results

Evidence synthesis, study characteristics and quality assessment

The literature search retrieved 1043 articles. After removing 160 duplicates, 883 studies were screened against title and abstract. Seven hundred sixty-seven studies irrelevant to our study were excluded. The full texts of the remaining 116 studies were screened, and 84 studies were further excluded. Finally, 32 studies were accepted and included for this systematic review and meta-analysis. Data extraction was done by three authors (PMM, MT and DRT). Figure 1 shows the PRISMA diagram.

Study characteristics are summarised in Table 1. The main study parameters and findings are outlined in Table 2. There were 12 cohort studies,[14-25] 5 case–control studies,[26-30] 9 cross-sectional surveys[31-39] and 6 case reports.[40-45] The total study population comprised 9371 participants including 2671 AAS users at various

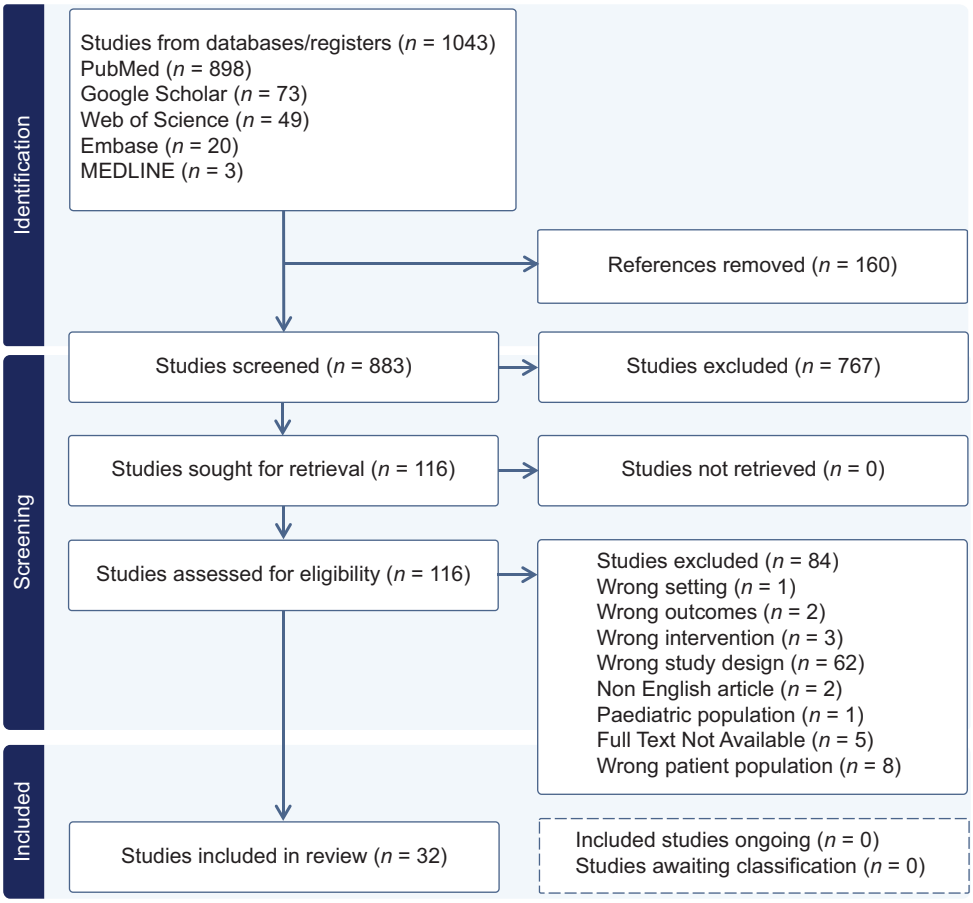

Figure 1: PRISMA diagram

stages of AAS use and the remaining AAS naïve control population. Table 2 also shows a detailed description of all the drugs used by the study population and the duration of use. As is evident from the data, most of the subjects used many compounds in various combinations and sequences. These compounds included testosterone and its various esters, nandrolone esters, stanozolol, metandienone, methyltestosterone, oxandrolone, mesterolone and various other compounds. In addition to these AAS, some subjects also used hormones such as growth hormones, antiestrogens, fertility agents, erectile dysfunction drugs and weight loss drugs. The doses used were quite a lot higher than the therapeutic doses of the compounds. Tables 3 and 4 show the quality assessment of the cohort and case–control studies, respectively, as per the NOS.[13]

Prevalence of anabolic-androgenic steroids use, its general health consequences and motivation to start anabolic-androgenic steroids

The estimated lifetime prevalence of AAS abuse is around 6% in men.[19] Adolescents and young adults are common users. The three times increased risk of mortality is a major health concern[19] with a reported prevalence of 18.3%–28.8% AAS use in gym clients.[35,38] Muscle development was the main motivator for using AAS. In addition, increased libido, improved sexual performance, virility and alleviated ageing process were the most cited reasons for starting or restarting AAS.[34] The incidence of AAS use reported in studies was variable. Coward *et al*.[33] reported a cohort of 382 men with profound hypogonadism (testosterone 50 ng/dl or less). Eighty (20.9%) of these had prior AAS exposure. AAS use was more common in men younger than 50 years, low education status and men who fathered less children. Many of the AAS users reported in various studies included in the current review practiced polypharmacy. Kovac *et al*. reported that very few users (15.2%) regret the AAS use despite side effects such as hypogonadism due to lack of awareness.[36] Despite the adverse effects, most of the AAS users were reluctant to seek medical help. In one survey, only 35.23% of respondents visited a doctor for concerns about AAS adverse effects.[39]

Effects on reproductive hormones: Meta-analysis and systematic review

Seven studies[15,22,26-30] comprising 327 participants compared the FSH in AAS users and naïve population. AAS users had significantly lower levels of

Table 1: Study characteristics

Study	Location	Study design	Total number of participants	AAS users (past, current, prospective)	AAS naïve (control)
Al Hashimi, 2022[14]	UAE	Cohort, descriptive	520	520	0
Alibegović, 2018[40]	Slovenia	Case report	1	1	0
Al-Janabi *et al*., 2011[15]	Iraq	Cohort study, observational	24	16	8
Armstrong *et al*., 2018[31]	Online	Cross-sectional online survey, descriptive cohort	231	213	0
Avant *et al*., 2018[32]	Online	Cross-sectional online survey, descriptive cohort	97	97	0
Bonetti *et al*., 2008[16]	Italy	Cohort, descriptive, prospective, observational	22	20	0
Boregowda *et al*., 2011[41]	UK	Case report	1	1	0
Coward *et al*., 2013[33]	USA	Cross-sectional survey	382	80	
Coxon, 2016[42]	UK	Case report	1	1	0
Flanagan and Lehtihet, 2015[17]	Sweden	Cohort, descriptive, prospective, observational	26	13	8
Gårevik *et al*., 2011[18]	Sweden	Cohort, descriptive, prospective, observational	26	26	
Harvey *et al*., 2022[34]	Multinational	Cross-sectional survey: Mixed methods study	133	113	
Horwitz *et al*., 2019[19]	Denmark	Cohort, retrospective matched	5995	545	5450
Ip *et al*., 2019[35]	USA	Cross-sectional survey	219	40	179
Kanayama *et al*., 2015[20]	USA	Cohort, cross-sectional, naturalistic	55	19	36
Karila *et al*., 2004[21]	Finland	Cohort, descriptive, prospective, observational	18	18	
Kovac *et al*., 2015[36]	USA	Cross-sectional survey	382	79	
Menon, 2003[43]	Malaysia	Case report	1	1	
O'Sullivan *et al*., 2000[26]	Australia	Case–control	58	41	17
Perry *et al*., 2005[37]	USA	Cross-sectional survey	207	207	
Pirola *et al*., 2010[44]	Italy	Case report	1	1	
Rahman *et al*., 2018[22]	Iraq	Cohort study, observational	20	12	8
Rasmussen *et al*., 2016*[27]	Denmark	Case-control, cross-sectional	100	70	30
Razavi *et al*., 2014[38]	Iran	Cross-sectional survey	250	72	
Shankara-Narayana *et al*., 2020[28]	Australia	Case–control (cross-sectional, observational study)	93	72	21
Sharef *et al*., 2017[29]	Iraq	Case–control	150	50	50
Smit *et al*., 2021[23]	Netherlands	Cohort prospective and observational	100	100	
Torres-Calleja *et al*., 2001[30]	Mexico	Case–control, observational	30	15	15
Urhausen *et al*., 2003[24]	Germany	Cohort	32	32	
Vilar Neto *et al*., 2018[45]	Brazil	Case report	1	1	
Windfeld-Mathiasen *et al*., 2021[25]	Denmark	Cohort retrospective matched	5995	545	5450
Zahnow *et al*., 2017[39]		Cross-sectional survey	195	195	
		Total	9371*	2671*	

*Horwitz 2019 and Windfeld-Mathiasen 2021 studies refer to the same population. AAS=Anabolic-androgenic steroid

FSH (SMD −4.61, 95% CI-6.50, −2.73, $P < 0.00001$). Effects of stopping AAS on FSH at various intervals were evaluated in different studies. Three months after stopping AAS (2 studies, 137 participants)[14,15] reported lower values of FSH, statistically insignificant from baseline at stopping AAS (SMD −12.67, 95% CI-38.16, 12.83, $P = 0.33$). At 6 months, three studies[14,18,21] with 216 participants reported still lower values of FSH in AAS users (SMD −1.00 CI-1.29, −0.70, $P = 0.003$). One year after stopping AAS, there was no significant difference between AAS users and the naïve population as reported in three studies[23,27,28] with 294 participants (SMD 0.02, 95% CI-0.34, 0.38, $P = 0.91$). Heterogeneity in all these studies was substantial, but lowest at 1-year follow-up. In 1-year analysis, the baseline population was the one who was yet to start AAS use in prospective observational study [Figure 2].

The study population reporting LH was the same as above. LH levels were significantly lower in AAS users compared to naïve (SMD −5.14, 95% CI-7.25, −3.04, $P < 0.00001$). At 3 months after stopping AAS, there were lower values of LH, statistically insignificant from baseline at stopping AAS (SMD −6.32, 95% CI-20.03, 7.38, $P = 0.37$). At 6 months, the LH values were lower (SMD −1.60, 95% CI-2.28, −0.91, $P < 0.00001$). At 1 year of stopping AAS, the LH values were statistically insignificant in AAS users and the naïve population (SMD −0.65, 95% CI-1.52, 0.22, $P = 0.14$).

Table 2: Main findings in the studies

Study	Study population description	Compounds used	Dose, duration	Main study parameters	Main findings
Al Hashimi, 2022[14]	AAS abusers in last 1 year complaining of sexual dysfunction and/or infertility	Non-prescribed AAS, hCG and CC	>1 year	Effects on sexual health and fertility, effects of treatment medications on early recovery	Significant negative impact on sexual health and fertility, medical TT causes faster recovery
Alibegović, 2018[40]	AAS abuser who committed suicide	Not mentioned	Unknown period of time		Shrunken testicles, absent spermatogenesis and very few Leydig cells
Al-Janabi *et al*., 2011[15]	Male body builders	MD, ND and TE	Not mentioned	Effects on semen analysis and hormone parameters	Profound effect on reproductive health
Armstrong *et al*., 2018[31]	Members of online bodybuilding forums	Undisclosed AAS, post-cycle therapy, AES, 17-alpha-alkylated hormones, cutting agents	Weekly doses of ≥600 mg/week in most subjects, duration <1–>10 years, most patients in 1–3 year group	Sexual function	Poorly defined long-term impact, higher T doses protective for ED functions
Avant *et al*., 2018[32]	Men attempting pregnancy	Not mentioned	Variable weekly doses, most subjects in 400–999 mg/week, duration <1–>10 years, most patients in 1–3 year group	Paternity rates	Unexpectedly high fertility rates due to cycling therapy and concomitant use of fertility preserving medicines
Bonetti *et al*., 2008[16]	Bodybuilders who continued to take AAS	ML, NL, ST, TS, AL, NAND, AN, DHEA, MST, MD, NAN, OX, TS + many concomitant drugs	Cumulative doses of 300–43,700 mg AAS, duration 6–51 weeks	Prospective evaluation of athletes who had never taken AAS before and starting voluntary AAS self-administration	Suppression of FSH, LH and SHBG. Reduction in spermatozoa count, fertility index
Boregowda *et al*., 2011[41]	Men evaluated for secondary infertility (patient had stopped AAS 2 years back)	NL, TS and GH	Dose not mentioned, duration >10 years	Evaluated for secondary infertility (patient had stopped AAS 2 years back)	Initially secondary gonadal failure resulting from anabolic steroid use with subsequent primary gonadal failure and infertility
Coward *et al*., 2013[33]	Men with hypogonadism	ND, ST, MD, TR, OX, OXM, DP, BO and ME	Duration 3–30 months	Hypogonadism	Prior AAS use is common in young men with hypogonadism
Coxon, 2016[42]	AAS user with infertility	Not mentioned	Not mentioned	Infertility	Infertility
Flanagan and Lehtihet, 2015[17]	Bodybuilders using AAS for 8–25 years	TS, NL, MD and ST	Median testosterone dose 2000 mg/week (750–6000 mg), duration 8–25 years	To study the HPG axis after chronic androgen abuse	GnRH and 72-h hCG stimulation is valuable in evaluation of the HPG axis in AAS abusers. Long-term AAS abusers have a pituitary dysfunction as well as a deceased Leydig cell responsiveness to hCG stimulation despite 7-month period of steroid washout
Gårevik *et al*., 2011[18]	Participants contacting anti-doping line	ND, TS + other	Not mentioned	Hormones FSH LH (side effects in a 12-month follow-up study in AAS abusers that were recruited to the study at cessation of their abuse)	Some individuals had a sustained suppression of LH and FSH for a period of 1 year

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Table 2: Contd...

Study	Study population description	Compounds used	Dose, duration	Main study parameters	Main findings
Harvey *et al*., 2022[34]	AAS users who identified libido and sexual function as reasons for starting and continuing non-prescribed AAS use	Not mentioned	Not mentioned	Libido and sexual function as reasons for starting and continuing AAS	Motivation to start or continue AAS: Increased libido, self-esteem, masculine identity
Horwitz *et al*., 2019[19]	Male subjects tested positive for AAS in Danish fitness centres	Not mentioned	Not mentioned	Long term survival (all-cause mortality) and somatic comorbidity (including 15 prescribed disorders) amongst AAS users versus control	Increased mortality risk, hospitalisation rate in AAS users. Side effects are a public health concern
Ip *et al*., 2019[35]	Gym clients in San Fransisco	CBT, GH, ABT, GHB, prohormone, AES, fertility agents, insulin, weight loss pills, EDP and OTC	Dose 1141±3287 mg/week, median: 400 mg (mean dose was 10 times higher and median dose 4 times higher than therapeutic dose)	Use of prescription drugs AAS- and non-AAS-using gym goers	Misuse of prescription drugs by gym goers, AAS users
Kanayama *et al*., 2015[20]	Weightlifters reporting at least 2 years of cumulative lifetime AAS use	Not mentioned	Supraphysiologic doses, at least 2 years, cumulative AAS dose mean 353,000 mg, (300,000 SD); cumulative lifetime AAS use 6.9 years mean (4.5 SD)	Physical examination, hormone determinations, IIEF	AAS withdrawal hypogonadism is common, prolonged and with morbidity
Karila *et al*., 2004[21]	Power athletes	MD, MS, OXM, ST, MT, OX, FM, MAN and TU, TS, NL, ML, ST, TR and BO	Cumulative dose 835–44,635 mg, duration 0.5–13 years	Effect of supraphysiological AAS with or without HCG on male fertility	Supraphysiological AAS combined with HCG lead to transient semen parameter impairment, spermatogenesis is usually maintained
Kovac *et al*., 2015[36]	Hypogonadal men	Not mentioned	Not mentioned	Regret about hypogonadism	15.2% of patients regretted AAS use, regret was unrelated to ASIH, side-effects. Fertility issues comparable
Menon, 2003[43]	Infertility, azoospermia, hypogonadotropic hypogonadism	TC, MD, OX, TP, OXM, ND and ME	Various doses, duration 10 years	Infertility treatment with HCG, HMG	AAS-induced azoospermia can be treated with hCG and hMG
O'Sullivan *et al*., 2000[26]	Past, current and potential AAS users	OXM, TS, BO, NL, MD, MA, ST and MAN	Various doses	Adverse effects	Adverse effects observed in AAS users, still they intended further use of AAS
Perry *et al*., 2005[37]	Visitors to fitness web pages	NL, TS, ST, BO, dietary supplements, CC, ANZ, CBT, T3, GH, insulin, TMX, hCG, MTF and finasteride	Various drugs mean dose 26.9 mg/day–583 mg/week	To know AAS regimens, types, doses, duration. Extent of dependence	AAS users use multiple agents, supplements. Polypharmacy, large dosages, substance abuse are health concerns

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Table 2: Contd...

Study	Study population description	Compounds used	Dose, duration	Main study parameters	Main findings
Pirola *et al*., 2010[44]	Chronic AAS abuser	NL, ST, MS, CC, hCG and BO	Cyclical therapy for 13 years	Hypogonadotropic hypogonadism	Hypogonadotropic hypogonadism
Rahman *et al*., 2018[22]	Athletes in two gymnasiums	TS and GH	Mixture 250 + 250 mg/day, for at least 6 months	Effect of AAS on hormones, haematological parameters and baldness	Hypogonadism and baldness
Rasmussen *et al*., 2016*[27]	Young men involved in recreational strength training	TES, TR, NL, ST, TICA, BO, DS, MA, OX, OXM, CL, GEST, MIB and AN	160–2000 mg/week, total duration geometric mean (95% CI): 142.3 (99.7–203.1) and 111.8 (81.3–153.7)	To evaluate effects of AAS on hormones and symptoms of hypogonadism	Past AAS users had lower testosterone, symptoms of hypogonadism. Current AAS abusers showed impaired spermatogenesis
Razavi *et al*., 2014[38]	Gym club members	TS, NL, OXM and other	Duration<6 weeks–12 years, most common group 25 months–12 years	Prevalence and patterns of AAS use	AAS use is common in adolescents and young adult bodybuilders, educated bodybuilders despite awareness of adverse effects
Shankara-Narayana *et al*., 2020[28]	Current and past AAS users	TES, AN, DHEA, 17α alkylated (MD, OX, OXM, OX, ST, CDMT, DNZ, MEPI, CMA, FM), non-17α alkylated (ML, MS, BO, DS, TR) and non-steroidal (specific androgen receptor modulators) synthetic androgens	Median duration 2.4 years	Recovery of male reproductive and cardiac function after stopping AAS	Supressed reproductive and cardiac function is recoverable
Sharef *et al*., 2017[29]	AAS users and two control groups	NL	200 mg/week for at least 3 months	Semen parameters	AAS users have abnormal shape sperms, low concentration, sluggish motility and infertility
Smit *et al*., 2021[23]	Men intending to start an androgen cycle	TES, TR, DS, TMX and CC	200 mg/week or more for at least 6 weeks	Speed and extent of testosterone production and spermatogenesis recovery	Testosterone production (by 3 months) and spermatogenesis (by 1 year) recover in majority
Torres-Calleja *et al*., 2001[30]	Body builders	OXM, MA, ND, TD, TP, MS, TE and TP	50–1500 mg/week for 8–16 weeks	Sperm morphology, hormones	High doses of AAS have adverse effects on endocrine and semen parameters, exercise by itself does not change these parameters
Urhausen *et al*., 2003[24]	Body builders and power lifters	BO, DS, FB, MA, NL, ST, TES, TR, DMT, FM, MS, MD, OX, OXM, ST, GH, CBT and anti-oestrogenes	Past: Mean dose 720 mg/week for 26 weeks/year over 9 years, current: Mean dose 1030 mg/week for 33 weeks/year over 8 years	Long term risk profile	Hormonal alterations due to long-term AAS abuse were reversible after stopping the medication for over 1 year

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Table 2: Contd...

Study	Study population description	Compounds used	Dose, duration	Main study parameters	Main findings
Vilar Neto *et al*., 2018[45]	Body builder	TS, NL and OXM	Cumulative 7000 mg over 8 weeks	To evaluate effect on HPG axis	Short time exposure to supraphysiologic doses of AAS causes severe disorder in HPG axis
Windfeld-Mathiasen *et al*., 2021[25]	Males who tested positive for androgens in an antidoping test program	Not mentioned	Not mentioned	Fertility	AAS abuse causes temporary reversible decline in fertility
Zahnow *et al*., 2017[39]	AAS users responding to the Global Drug Survey 2015	AAS and PED	Not mentioned	Factors associated with health service engagement and treatments related to service satisfaction amongst of AAS users	Non-judgmental health services aimed at assisting AAS users is needed

ABT=Albuterol, salbutamol, AES=Anti-oestrogens, AL=Androstenediol, AN=Androstenedione, ANZ=Anastrozole, BO=Boldenone/boldenone undecylenate/boldenone undecenoate, CBT=Clenbuterol (sympathomimetic amine), CC=Clomiphene, CDMT=Chlorodehydromethyltesto sterone, CL=Clostebol, CMA=Chloromethylandrostenediol, DHEAS=Dehydroepiandrosterone, DMT=4-dehydrochlormethyltestosterone, DNZ=Danazol, DP=Drostanolone propionate, DS=Drostanolone, EDP=Erectile dysfunction medications, FB=Formebolone, FM=Fluoxymesterone, fluxymesterone, GEST=Gestrinone (dimetrose/nemestran), GH=Growth hormone, GHB=Gammahydroxybutyrate, hCG=Human chorionic gonadotrophin, MA=Methenolone acetate, metenolone, metenolone acetate, MAN=Methylandrostenedione, methandriol, MD=Methandienone/methandrostenolone/metandienone (dianabol), ME=Methenolone enanthate, MEPI=Methylepitiostanol, MIB=Metribolone, ML=Methenolone, MS=Mesterolone, MST=Mestanolone/methylandrostanolone/androstalone, MT=Methyltestosterone, MTF=Metformin, NAN=Norandrostenedione, NAND=19-nor-4-androstenedione, ND=Nandrolone decanoate, NDE=Nandrolone esters, NL=Nandrolone, OTC=Over the counter medicines, OX=Oxandrolone, OXM=Oxymetholone, oxymetholome, oximetalone (anadrol, anapolon), PED=Performance enhancing drugs, ST=Stanozolol, T3=Liothyronine, TC=Testosterone cypionate, TD=Testosterone decanoate, TP=Testosterone propionate, TE=Testosterone enanthate, TES=Testosterone esters, TICA=Testosterone isocaproate (Sustanon), TMX=Tamoxifen, TN=Testosterone nicotinate, TR=Trenbolone, TS=Testosterone, TU=Testosterone undecanoate, AAS=Anabolic-androgenic steroid, TT=Total testosterone, FSH=Follicle-stimulating hormone, LH=Luteinising hormone, HPG=Hypothalamo–pituitary–gonadal, GnRH=Gonadotrophic releasing hormone, IIEF=International Index of Erectile Function, CI=Confidence interval, SD=Standard deviation, SHBG=Sex hormone binding globulin, ASIH=Anabolic steroid induced hypogonadism, hMG=Human menopausal gonadotropin

There was substantial heterogeneity in all these data [Figure 3].

Six studies[15,22,27-30] comprising 303 participants compared the TT in AAS users and naïve population. In some studies, the TT was higher in AAS users and in some lower. The overall effect was not significant (SMD 1.27, 95% CI-0.95, 3.50, $P = 0.26$), with substantial heterogeneity. At 3 months (2 studies, 137 participants),[14,15] TT values were not significantly different from baseline (SMD −1.78, 95% CI-5.71, 2.16, $P = 0.38$), with substantial heterogeneity. Similarly, at 6 months (2 studies, 148 participants),[14,21] the results were almost the same (SMD 0.99, 95% CI-1.07, 3.06, $P = 0.35$). One year after stopping AAS use (3 studies, 294 participants),[23,27,28] AAS users had lower TT values compared with the naïve population (SMD 0.73, 95% CI-0.49, 0.97, $P < 0.00001$), negligible heterogeneity [Figure 4].

Although most of the studies report normalisation of the hormonal milieu by 1 year of AAS abstinence, Coxon[42] reported a case of hypogonadism persisting 3 years after stopping AAS. Similarly, Boregowda *et al*.[41] reported a 40-year-old male who developed prolonged and irreversible gonadal failure and infertility after AAS use. This patient presented with erectile dysfunction and secondary gonadal failure in the form of low levels of FSH, LH and TT 2 years after stopping AAS. At 30-month follow-up, he had features of secondary gonadal failure. Flanagan and Lehtihet[17] reported dysfunction of hypothalamo–pituitary–gonadal axis (HPG) in the form of attenuated response to gonadotrophic releasing hormone and human chorionic gonadotropin (hCG) stimulation tests despite an AAS washout period of 7 months. Urhausen *et al*.[24] also reported recovery of HPG axis hormones over 1 year of stopping AAS.

Observational studies on AAS users followed prospectively and periodically are rare. Smit *et al*.[23] followed up 100 men voluntarily intending to start an androgen cycle. The baseline values of FSH and LH were 3.9 and 3, respectively. These values dropped at the cycle end to 0.1 and 0.1; recovering to 3.2 and 2.8 at 3 months and 4.1 and 3.1 at 1 year, respectively (all values are

Table 3: Quality assessment of cohort studies as per the Newcastle–Ottawa Scale

Cohort studies	Selection				Comparability (**)	Outcome		Adequacy of follow-up (*)	Total (9*)
	Representativeness of exposed cohort (*)	Selection of non-exposed cohort (*)	Ascertainment of exposure (*)	Demonstration that outcome of interest was not present at start of study (*)		Assessment of outcome (*)	Follow up duration (*)		
Al Hashimi, 2022[14]	*	-	*	*	-	*	*	*	6*
Al-Janabi *et al*., 2011[15]	*	*	*	*	**	*	*	*	9*
Bonetti *et al*., 2008[16]	*	-	*	*	-	*	*	-	5*
Flanagan and Lehtihet, 2015[17]	*	*	*	*	**	*	*	*	9*
Gårevik *et al*., 2011[18]	*	-	*	*	-	*	*	*	6*
Horwitz *et al*., 2019[19]	*	*	*	*	**	*	*	*	9*
Kanayama *et al*., 2015[20]	*	*	*	*	**	*	*	*	9*
Karila *et al*., 2004[21]	*	-	*	*	-	*	*	*	6*
Rahman *et al*., 2018[22]	*	*	*	*	**	*	-	-	7*
Smit *et al*., 2021[23]	*	-	*	*	-	*	*	-	5*
Urhausen *et al*., 2003[24]	*	*	*	*	**	*	-	-	7*
Windfeld-Mathiasen *et al*., 2021[25]	*	*	*	*	**	*	*	*	

Table 4: Quality assessment of case–control studies as per the Newcastle–Ottawa Scale

Case control studies	Selection				Comparability: Comparability of cases and controls (**)	Exposure			Total (9*)
	Adequate definition (*)	Representativeness of the cases (*)	Selection of controls (*)	Definition of controls (*)		Ascertainment of exposure (*)	Same method of ascertainment for cases and controls (*)	Non-response rate (*)	
O'Sullivan *et al*., 2000[26]	*	*	-	*	*	*	*	*	7*
Rasmussen *et al*., 2016[27]	*	*	*	*	*	*	*	*	8*
Shankara-Narayana *et al*., 2020[28]	*	*	*	*	*	*	*	*	8*
Sharef *et al*., 2017[29]	*	*	*	*	*	*	*	*	8*
Torres-Calleja *et al*., 2001[30]	*	*	*	*	*	*	*	*	8*

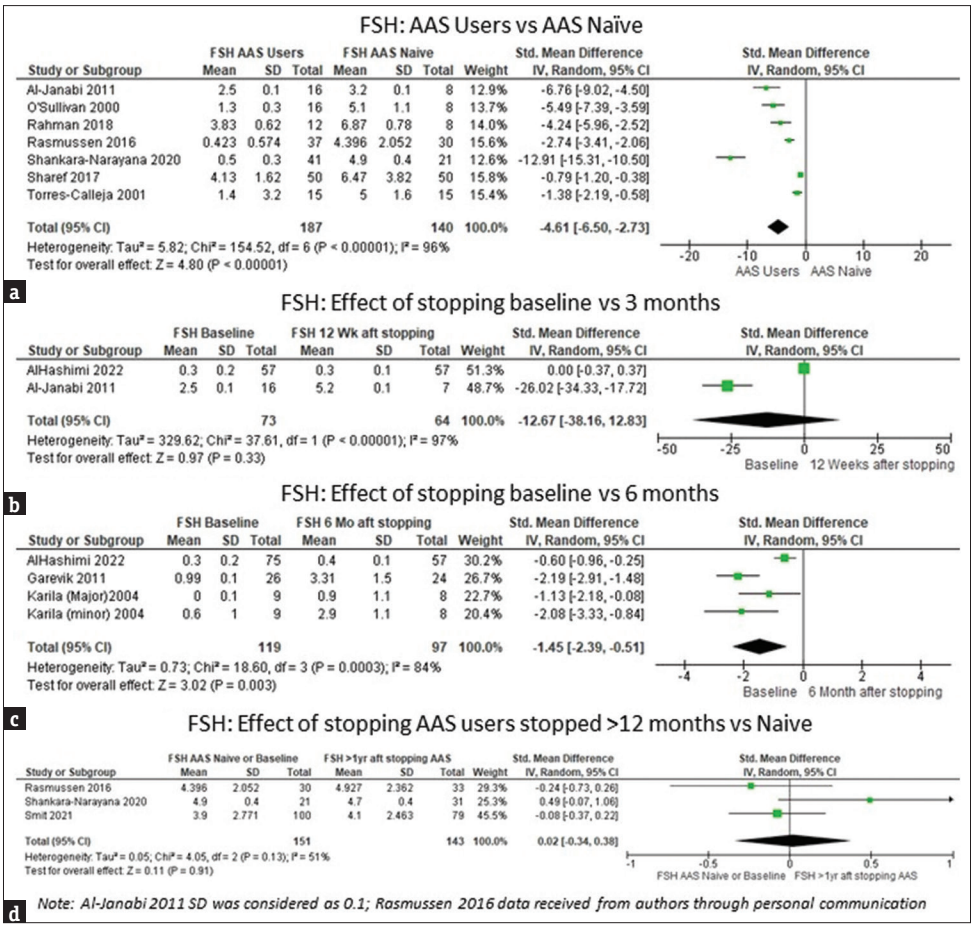

Figure 2: Meta-analysis of follicle-stimulating hormone at various time intervals. FHS: Follicle-stimulating hormone, AAS: Anabolic-androgenic steroids

mean in mIU/ml). TT values at baseline, end of cycle, 3 months and 1-year testosterone levels were 10.60, 23.01, 4.26 and 4.49 ng/ml, respectively. Vilar Neto *et al*.[45] published a case report of a young healthy man who developed complete HPG axis derangements after 8 weeks of starting supraphysiological doses of AAS. The recovery of hormonal parameters usually happens by 1 year, but not always.[42] It is possible that factors such as age, dose and duration of AAS abuse may play a role in the persistence of hypogonadism. This is more important in men desiring fertility.

Effects on semen parameters, testis size, erectile function and fertility rates: Meta-analysis and systematic review

Three studies (n = 154) reported sperm concentration[15,29,30] and three (n = 186) reported motility.[15,28,29] Sperm concentration was lower in AAS users, but the overall effect was not significant (SMD −1.27, 95% CI-2.84, 0.30, P = 0.11), with considerable heterogeneity. Karila *et al*. reported a weak negative correlation between mean daily AAS dose and sperm concentration.[21] In studies reporting sperm motility, sperm motility was significantly lower in AAS users (SMD −2.72, 95% CI-5.46, 0.02, P = 0.05), with considerable heterogeneity [Figure 5].

Testis size (measured by orchidometer) in AAS users and naïve population was reported in three studies comprising 170 participants.[20,27,28] The testis size was significantly smaller in AAS users as compared to the naïve population (SMD −3.92, 95% CI-7.65, −0.18, P = 0.04). Heterogeneity was considerable. Bonetti *et al*.[16] reported effect of continued use of AAS over 2 years. The results from the right and left sides were reported separately. Over 2 years, there was a significant reduction in testis size as compared to baseline values (SMD 0.71, 95% CI 0.16, 1.26, P = 0.01), with considerable heterogeneity [Figure 6]. Alibegović[40] reported a case of AAS user who committed suicide due to aggressive behaviour and physical abuse of his wife. He had signs of secondary hypogonadism with bilateral shrunken testes and absent spermatogenesis, parenchymal sclerosis and very few Leydig cells. Another patient reported by Boregowda *et al*.[41] had bilateral testicular atrophy and azoospermia which showed modest and slow recovery. A cross-sectional survey of 231 AAS abusers by Armstrong *et al*.[31] revealed improved International

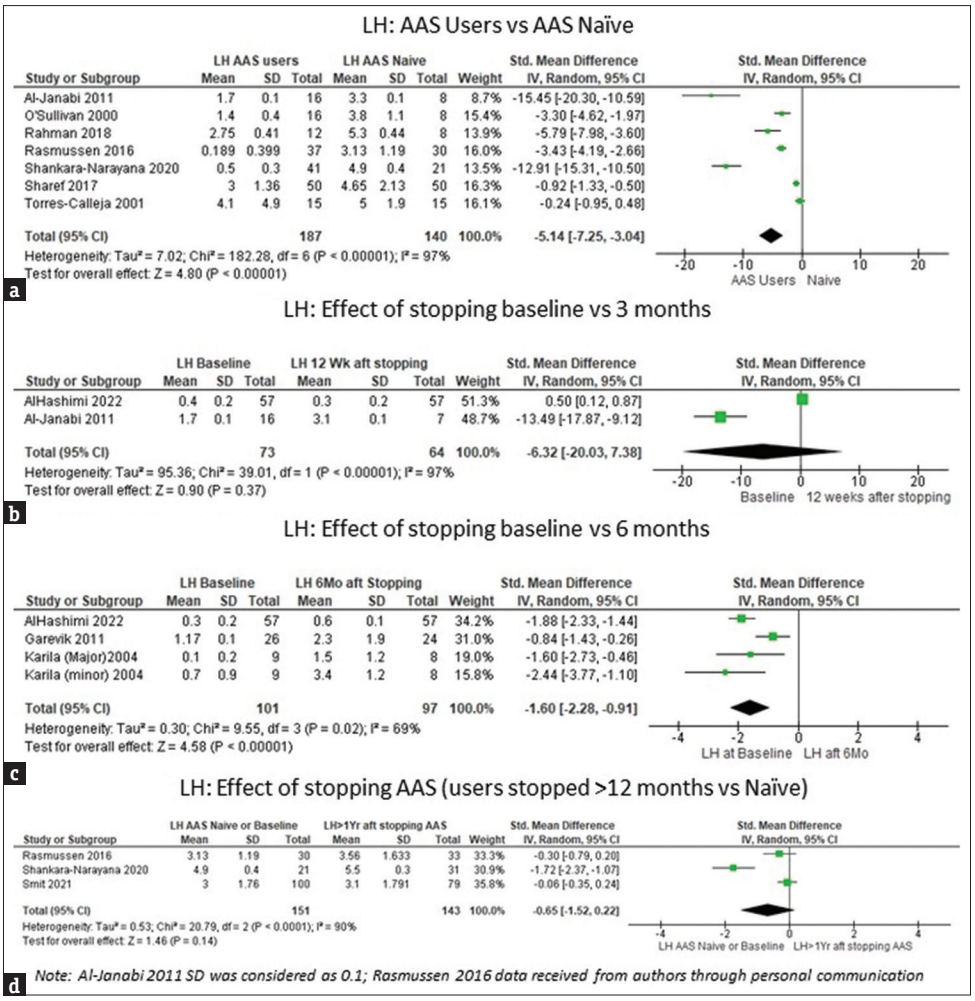

Figure 3: Meta-analysis of luteinising hormone at various time intervals. LH: Luteinising hormone, AAS: Anabolic-androgenic steroids, CI: Confidence interval

Index of Erectile Function-5 scores with increasing doses of AAS, but on withdrawal of AAS, these subjects had decreased libido and erectile dysfunction. This effect was more pronounced in frequent and long-duration AAS abusers.

Our review found the incidence of male infertility in AAS users between 11%[33] and 18%.[14,32] To mitigate the effects of AAS on fertility, most of the AAS users use washout periods and ancillary medications such as phosphodiesterase inhibitors as sexual enhancement medications (SEMs) and antiestrogens to maintain fertility. These measures lead to incomplete suppression of the HPG axis. In one cross-sectional survey reported by Avant *et al*.,[32] 94.8% of users consumed ancillary medications such as phosphodiesterase inhibitors, dopamine agonists (SEM) and other medications. This led to unexpectedly high self-reported fertility rates of 92.8% in the study population. Menon reported a case of a 37-year man who presented with azoospermia 1 year after stopping AAS. This man was successfully treated with hCG and hMG.[43] In one retrospectively matched cohort study, the[25] fertility rate amongst AAS users over the prior 10 years was reported 26% lower (relative risk [RR] 0.74; 95% CI-0.60, 0.90; $P = 0.0028$). Following the doping sanction, the fertility rate improved dramatically and was only 7% lower than the control cohort (RR 0.93, 95% CI-0.84, 1.03). There was no difference in the need for assisted reproductive techniques in the two cohorts.

A prospective observational study[23] of men voluntarily starting AAS reported an initial decline in semen volume, sperm concentration, total sperm count, progressive motility, total motile sperm count and mean testicular volume at the end of cycle and 3-month follow-up and recovery by 1 year. Through the hormone parameters recover by 3 months, spermatogenesis recovery is expected after 1 year.[23]

Systematic review of other findings

Around three-quarters of AAS users experienced improved quality of life while on AAS

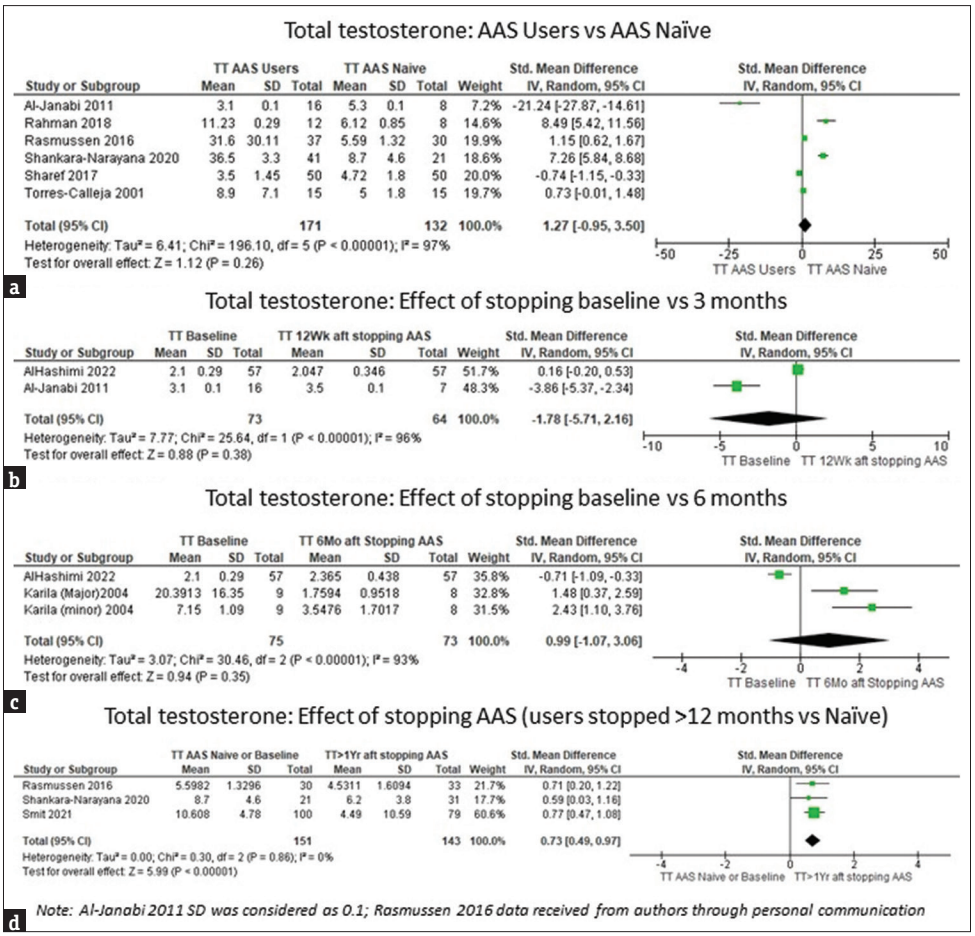

Figure 4: Meta-analysis of total testosterone at various time intervals. AAS: Anabolic-androgenic steroids, CI: Confidence interval

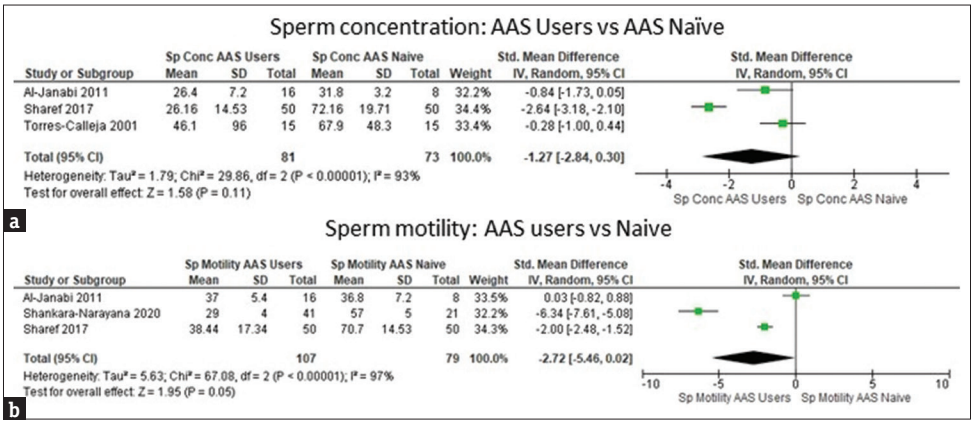

Figure 5: Meta-analysis of semen parameters. AAS: Anabolic-androgenic steroids, CI: Confidence interval

use.[34] Some experience aggressive behaviour and fluid retention.[33] On withdrawal, they experience low mood, gynaecomastia, loss of sexual desire, ED, reduced orgasmic satisfaction, ejaculatory disorders and combinations of different sexual symptoms.[14] In addition to various reproductive side effects, reported acne has been one of the troublesome issues reported in 35%–40% of individuals.[19,26,33,37]

Discussion

The use of AASs has long been a subject of medical and social scrutiny. Our comprehensive systematic review and meta-analysis has further expanded the understanding of AAS's impact on male fertility parameters. The main findings of our meta-analysis and systematic review are significantly lower levels of FSH and LH in AAS users. Three months after discontinuing AAS, there were

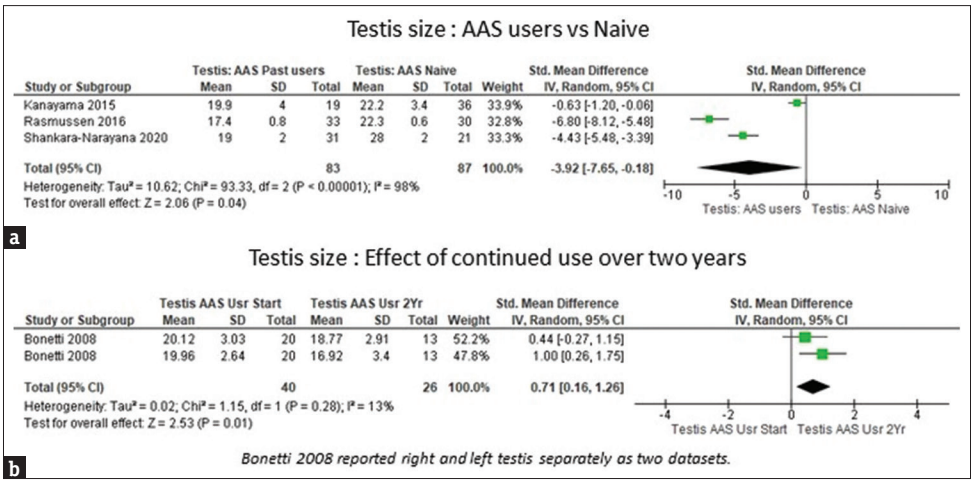

Figure 6: Meta-analysis of testis size. AAS: Anabolic-androgenic steroids, CI: Confidence interval

statistically insignificant reductions in FSH and LH values. However, at 6 months post-discontinuation, FSH and LH levels were significantly lower. Interestingly, 1 year after cessation of AAS, there was no significant difference observed between AAS users and the naïve population. Some studies reported higher TT levels in AAS users, while others reported lower levels; however, the overall effect was not significant. Three months and six months after discontinuation, TT values were not significantly different from baseline. Yet, 1 year after discontinuation, AAS users exhibited lower TT values compared to the naïve population. In terms of semen parameters, AAS users demonstrated low sperm motility, and they also exhibited reduced testicular size. However, caution is advised in interpreting the results, as many of them exhibit wide confidence intervals and significant heterogeneity.

Significant reductions in FSH and LH levels during AAS use were also reported in earlier reviews on this topic.[8,9] Earlier review on this subject by Christou *et al*. has reported on fertility outcomes and reversibility.[8] However, the Christou *et al*.[8] review did not include unexposed population.[9] Moreover, some of the studies included in Christou *et al*. meta-analysis were older studies wherein the doses of the AAS used were almost therapeutic doses,[46-51] whereas some included studies had subjects consuming supraphysiologic AAS doses.[16,21,52-54] In our meta-analysis, the effects on TT were inconclusive as the studies included men consuming AAS with or without testosterone. This was addressed by Christou *et al*. wherein the effect of testosterone-containing regimen and regimen without testosterone was analysed separately. Such subgroup analysis was not possible in our meta-analysis as interventional studies with sole agents were scant in our review. Christou *et al*. review also included some studies with female subjects. This issue was addressed in a recent systematic review and meta-analysis published by Corona *et al*.[9] wherein the authors included studies with male participants and most studies with supraphysiologic doses and few with therapeutic doses. In our review, we included studies with male subjects taking supraphysiologic doses of AAS. Moreover, most of the studies included in our meta-analysis[20,22,26-30] had a control unexposed population. The study population included in our review is representative of the current real-world epidemic of AAS use in society wherein athletes as well as amateur individuals are taking many drugs in supraphysiologic doses without medical supervision.

The association of AAS and infertility has been a concern for a long time. As there are no systematic investigations of the effects of doping with high-dose AAS on testicular function, contraceptive trials may serve as a model for what happens under AAS suppression. Of 1549 healthy eugonadal men who participated in 30 different clinical trials, after cessation of medication, 67% showed a return to sperm concentrations above 160 million/ml within 6 months, 90% within 12 months, 96% within 16 months and 100% within 24 months.[55] Thus, a 6–24-month span provides a time frame for recovery in AAS abusers, although it must be kept in mind that doses used for doping far exceed those used for male contraception, and therefore, an even longer recovery period may be anticipated. Our findings also delve into the gradual reversibility of AAS-induced fertility issues. Recovery time is 1 year in most of the studies. However, the recovery time is variable in anecdotal case reports from 2½ years to 3 years.[39,40] The recovery is not uniform across different studies as it may be influenced by factors such as duration and intensity of AAS use, as well as age. These variables are not strictly controlled in

the included studies in this review. Non-uniform study population, observational nature of the studies included in our review and variable duration, type and dose of the AAS use may be a plausible reason for these findings.

Widespread use of AAS use and concerns about associated health risks and ethical considerations led to the International Olympic Committee (IOC) banning its use in Olympic competitions.[49,50,51,57] In the last few decades, the relationship between testosterone and muscle strength and exercise training has been established, but concerns for long-term safety persist.[58] Despite the legal restrictions and health risks associated with AAS use, their use remains widespread and prevalent amongst athletes both in competitive sports and non-competitive leisure and fitness sports, military, police officers and even high school and university students.[59,60] The overall global lifetime prevalence rate of AAS use amongst male athletes is around 3.3%.[61]

The introduction of legislation banning the sale and use of AAS by most European countries and sporting agencies led to the development of black market and counterfeit products.[56] Most users now obtain the products locally from unlicensed pharmaceuticals or from online sites[56,62,63] or over the counter without the need for a doctor's prescription.[56] The pattern of use of these drugs varies considerably because they are mostly self-administered and largely unsupervised by physicians since the drugs are illegal. These include taking escalating doses in cycles over 6–12 weeks ('pyramiding'), combining two or more steroids ('stacking') and use of multiple AAS in overlapping patterns to avoid tolerance ('plateauing'). Polypharmacy dependency involves combining medications to mitigate side effects and maximise AAS action. Various agents used are growth hormone and insulin for additional anabolic effect, hCG to counteract the reduction in testicular size resulting from high-dose androgen use, an aromatase inhibitor to counteract gynaecomastia, a 5-alpha reductase inhibitor to prevent balding and acne that occurs with exogenous androgens and diuretics to promote water loss and prevent weight gain ('arraying').[60,63,64] AAS does have an important clinical therapeutic application such as androgen replacement in hypogonadism, to induce puberty and also in the treatment of chronic degenerative diseases,[10] chronic catabolic disorders such as anaemia and muscle wasting secondary to haemodialysis, COPD or HIV[65-67] and relief of the bone pain accompanying osteoporosis.[68]

In the current review, we found that the motivating factors for starting AAS were muscle development, increased libido, improved sexual performance, virility and alleviated ageing process. The implications of the effects of AAS are manifold. For health care providers, it underscores the need for a nuanced approach to treating patients who have a history of AAS use. General recommendations may not suffice, and personalised treatment plans could be more effective. As AAS use is viewed negatively, a non-judgmental healthy and trusting physician–patient relationship is vital in the management. The patient should be counselled to stop all AAS as well as any self-administered ancillary drugs and supplements. For severely symptomatic patients, a 4-week tapered course of transdermal or injectable testosterone replacement therapy may provide immediate symptom improvement.[69] Conservative or medical management forms the initial protocol for the management of AAS-induced male infertility. For patients with histopathological abnormalities (namely, sperm maturation arrest), IVF-ICSI has been used but there is no published data confirming the success. Microdissection testicular sperm extraction (micro-TESE) may be used for the exceedingly rare case of unrelenting azoospermia that does not resolve despite a thorough attempt at medical treatment. HCG is known to preserve testicular function and prevent testicular atrophy. AAS-induced sexual dysfunction and hypogonadism are more common, usually temporary and require treatment with testosterone replacement therapy, SERMs and PDE5 inhibitors. The current review has shown that higher T doses are protective for erectile functions during their use, but there can be decreased libido and ED after discontinuing T.[31] Cycling of the therapy and concomitant use of fertility-preserving medicines also preserves fertility in these patients.[32] As most of the AAS use is uncontrolled and unregulated, the exact effect on fertility is difficult to evaluate.

The present review suggested that men who are unaware of negative impact of AAS on fertility are likely to regret AAS use.[36] Prevention of AAS use through community education is a need of the time. Bates *et al*.[70] have suggested strategies for the prevention of AAS use. Most of the preventive strategies are practiced in sporting domains. Preventive interventions have socioecological strategies involving ethics, principles, values, social norms, body image and healthy alternatives aimed at bodybuilding. Public awareness campaigns, meeting with prior AAS users and online social media platforms would be appropriate platforms to disseminate necessary preventive information. In addition, health care providers also need to be educated about side effects of AAS and precise diagnostic testing. Similarly, the chemists also need to be educated about the undercover sale of AAS as prodrugs. Government and regulatory authorities also

need to be sensitised about the necessary regulations and legislations.[71]

Strength

Our studies strength lies in a comprehensive review of 32 publications systematically reviewed that specifically attempt to outlay the negative effects on the fertility of AAS users. The study population being 9371 individuals, of which 2671 were AAS users. We have aimed to include all data wherein data about human subjects are available, including the case reports. Furthermore, this article also presents meta-analysis of reproductive hormones, semen parameters and testis size.

Limitations

This meta-analysis has several limitations that should be considered. First, most of the included studies were observational, which makes it challenging to establish causation definitively. Second, many studies had small sample sizes. The AAS use was unregulated and unsupervised AAS use and subjects in some studies resorted to polypharmacy. Third, the lack of information on dosing limits us from making further recommendations on the same. Although the studies rate good on the NOS, the domains used are not univocal and there are some inherent limitations in using NOS for meta-analysis. Importantly one should also note that there was considerable heterogeneity and wide confidence intervals amongst the studies, which may be attributed to variations in study design, AAS dosages and duration of use. In addition, the long-term effects of AAS on male fertility remain inadequately studied, as some studies focused on short-term outcomes only. Finally, publication bias may exist. Various confounding factors as would be evaluated in standard clinical trials are not taken into consideration. Hence, we do accept that whilst estimates of the fertility issues are adequately available, they can only be taken at face value.

Conclusion

While AAS use for performance enhancement is not a new phenomenon, it has detrimental impact on male fertility parameters such as reduced gonadotropin levels and sperm concentration. Sperm motility was also lower along with smaller test size in AAS users. The ill effects on fertility may be partly reversible. Our systematic review and meta-analysis contribute to this evolving narrative, urging both the medical community and the public to consider the multifaceted implications of AAS use. However, our results should be interpreted with caution since most results show wide CI and significant heterogeneity.

Author's contributions

PMM - Concept, literature search, data acquisition and analysis, manuscript preparation, editing and review; PNM - Concept, literature search, data acquisition, manuscript preparation, editing and review; VG - Concept, literature search, data acquisition, manuscript preparation, editing and review; SGA - Literature search, data acquisition, and manuscript preparation; MT - Literature search, data acquisition and analysis, and manuscript preparation; AGS - Literature search, data analysis, and manuscript preparation; GRT - Literature search, data acquisition and analysis, and manuscript preparation; USS - Concept, literature search, data acquisition and analysis, and manuscript preparation; DPS - Concept, literature search, and manuscript preparation; DM - Concept, literature search, and manuscript preparation.

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Conflicts of interest

There are no conflicts of interest.

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