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Original Research

Factors predicting normalization of reproductive hormones after cessation of anabolic-androgenic steroids in men: a single center retrospective study

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Abstract

Objective: Symptomatic hypogonadism discourages men from stopping anabolic-androgenic steroids (AAS). Some men illicitly take drugs temporarily stimulating endogenous testosterone following AAS cessation (post-cycle therapy; PCT) to lessen hypogonadal symptoms. We investigated whether prior PCT use was associated with the normalization of reproductive hormones following AAS cessation.

Methods: Retrospective analysis of 641 men attending a clinic between 2015-2022 for a single, nonfasting, random blood test <36 months following AAS cessation, with or without PCT. Normalized reproductive hormones (ie, a combination of reference range serum luteinizing hormone, follicle-stimulating hormone, and total testosterone levels) were the surrogate marker of biochemical recovery.

Results: Normalization of reproductive hormones was achieved in 48.2% of men. PCT use was associated with faster biochemical recovery (13.0 (IQR8.0-19.0) weeks, PCT; 26.0 (IQR10.5-52) weeks, no-PCT; $P < .001$). Odds of biochemical recovery during multivariable analysis were: (1) higher with PCT (OR3.80) vs no-PCT ($P = .001$), in men stopping AAS ≤3 months previously; (2) reduced when 2 (OR0.55), 3 (OR0.46), or 4 (OR0.25) AAS were administered vs 1 drug ($P = .009$); (3) lower with AAS >6 vs ≤3 months previously (OR0.34, $P = .01$); (4) higher with last reported AAS >3 months (OR 5.68) vs ≤3 months ($P = .001$). PCT use was not associated with biochemical recovery in men stopping AAS >3 months previously.

Conclusion: Without evidence-based withdrawal protocols, men commonly try avoiding post-AAS hypogonadism with PCT, which is illicit, ill-defined, and not recommended. Only half of men had complete biochemical testicular recovery after stopping AAS. The surprising association of self-reported PCT use with short-term biochemical recovery from AAS-induced hypogonadism warrants further investigation.

Keywords: anabolic-androgenic steroids, androgens, hypogonadism, post-cycle therapy, testosterone, withdrawal

Significance

Anabolic-androgenic steroids (AAS) are increasingly being used worldwide for their potent effect on muscle development. AAS suppresses testosterone secretion and men may experience hypogonadal symptoms upon cessation. There is no evidence-based approach to AAS withdrawal, and many men self-administer post-cycle therapy to reduce symptoms. A retrospective multivariable analysis of 641 attending for a blood test <36 months following AAS cessation, with or without post-cycle-therapy (PCT), showed odds of recovery were higher with PCT use when stopping AAS ≤3 months previously and with last reported AAS <3 months. Recovery was lower with greater AAS use and AAS use >6 months. PCT is illicit, ill-defined, and not recommended. The association of PCT use with recovery from AAS-induced hypogonadism suggests further studies are needed.

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Introduction

Anabolic-androgenic steroids (AAS) are highly potent, illicit drugs used for their direct or indirect actions to increase muscle development. AAS use has been reported to increase the risk of death, cardiomyopathy, stroke, severe mental illness including psychosis, transmission of blood-borne viruses, and violent behavior.[1-6] The Crime Survey of England and Wales estimated that 411 000 men (2% of the UK male population) admitted to recently using AAS; similar prevalence has been reported in the United States and other countries.[7-10]

Exogenous AAS suppress endogenous testosterone, and their cessation is associated with reduced testosterone and gonadotrophin secretion.[2,11,12] Studies suggest that it may take months or years for some to recover testosterone secretion following cessation of AAS.[2,11-14] As a result, men may experience diminished libido, poor erections, tiredness, weakness, depressive symptoms, and suicidal ideation.[11-13,15-17] Unsurprisingly, men experiencing these severe withdrawal symptoms following cessation often resume AAS, leading to an increased risk of developing dependence.[17-19] Other addictive substances such as heroin, benzodiazepines, alcohol, and nicotine have recommended drug treatments proven to reduce withdrawal symptoms.

There is currently no evidenced-based therapeutic approach to facilitate safe withdrawal from AAS. Some endocrinologists advise simple cessation of AAS. It is important to investigate whether alternative therapies can temporarily reduce withdrawal symptoms in men ceasing AAS use, without prolonging recovery of testicular function. Development of such therapies would allow men access to behavioral interventions to reduce risks of relapse.

Many men using AAS illicitly self-administer post-cycle-therapy (PCT) to stimulate endogenous testicular function when transitioning from AAS use to cessation, in an attempt to prevent or relieve hypogonadal symptoms.[2,20,21] PCT is a colloquial, nonmedical term used by men using AAS to describe a heterogeneous group of nonprescribed substances used in varying regimes. PCT typically comprises a 2-to-12-week course of human chorionic gonadotrophin (hCG), and/or selective estrogen receptor modulators (SERM) or aromatase inhibitors (AI).[21] hCG directly stimulates endogenous testosterone secretion within the testes, while SERMs and AIs indirectly stimulate testosterone secretion by inhibiting estrogenic feedback on hypothalamus GnRH and pituitary gonadotrophin secretion. hCG, SERMs, and AIs have been reported to potently stimulate endogenous testosterone and gonadotrophin secretion when treating men with infertility and/or hypogonadism.[22-24] There is growing literature on PCT, and user characteristics associated with PCT use, but there is limited data investigating the interactions of PCT with recovery of testicular function following AAS cessation; such studies are important since PCT drugs have powerful effects either prolonging or promoting recovery from AAS.[20,25-29]

Glasgow is a city in Scotland with some of the highest rates of social deprivation, crime, and substance misuse rates within the UK.[30] We conducted the largest ever retrospective study of PCT use, auditing clinical and biochemical parameters in over 600 users stopping AAS in Glasgow since 2015, attending a single harm reduction clinic providing drug awareness, health promotion, and blood-borne virus testing. All data was collected within the clinic using the same questionnaire. Our study aimed to investigate how many men stopping AAS achieve normalization of reproductive hormones with and without the use of PCT.

Materials and methods

Study design and governance

A retrospective analysis of men who had undergone a post-AAS cycle assessment between 2015 and 2022 at the Glasgow Image and Performance Enhancing Drug Clinic was performed. This was a voluntary, community-dwelling, needle-exchange clinic as part of a public health network to support AAS users. Audit approval was received from the Associate Medical Directorate of Glasgow Alcohol and Drug Recovery Services on December, 14, 2021 with the aim of determining how many men stopping AAS have recovered their testosterone following the use of PCT. Caldicott Guardian approval from the Greater Glasgow and Clyde NHS Trust was approved on February, 23, 2022 on the conditions of, supervised and anonymized data collection, randomized patient lettering, and use of age, not date of birth. Data were collected using paper and computer records which were held at the Glasgow Image and Performance Enhancing Drugs Clinic.

Study population

A total of 807 men attended the clinic during this time; data was excluded for repeat attendances, missing gonadotrophin, or testosterone results, or insufficient documentation to determine whether PCT was used. Men with testosterone >36 nmol/L and luteinizing hormone (LH) > 12 U/L (upper limits of reference range) were excluded to avoid possible current AAS use or PCT use respectively. Individuals self-reporting AAS or PCT use within the last 1 week were excluded. Those ceasing AAS for >156 weeks were excluded (4 men, range 5-29 years). Following these exclusions, a total of 641 men were included in the analysis; 170 had not used PCT and 471 had used PCT (Figure 1).

Data collection

Retrospective clinical data was extracted using standardized questionnaires of age; duration of AAS cycle; time since last AAS; type of AAS; use of other image and performance-enhancing drugs; use of PCT; PCT drugs used. Biochemistry data collected included serum LH (reference range: 1-12 U/L), follicle-stimulating hormone (FSH) (reference range: 1-12 U/L), total testosterone (reference range: 10-36 nmol/L), sex hormone binding globulin (SHBG), and albumin. Semen samples were not collected. Testosterone, LH, FSH, and SHBG assays were performed on the Abbott ARCHITECT system with an assay coefficient of variability (CV) of ≤10%. The ARCHITECT 2nd generation testosterone assay (Abbot Cat# 2P13, RRID: AB_2895254) had a lower limit of quantification (LoQ) of ≤0.15 nmol/L and the ARCHITECT LH assay (Abbott Cat# 2P40-25, RRID:AB_2813909) had a LoQ of ≤0.5 IU/L. The ARCHITECT FSH assay (Abbott Cat# 7K75-25, RRID: AB_2813910) had an analytical sensitivity of better than 0.05 IU/L and ARCHITECT SHBG assay (Abbott Cat# 8K26, RRID:AB_2895255) analytical sensitivity of ≤0.1 nmol/L. Regular internal quality checks are undertaken in the laboratory, and it is subject to U.K. National External Quality Assurance Service monitoring. Data collection was complete in all included men for the following categories of data: age; use of PCT; total testosterone; LH; FSH but incomplete for: AAS cycle

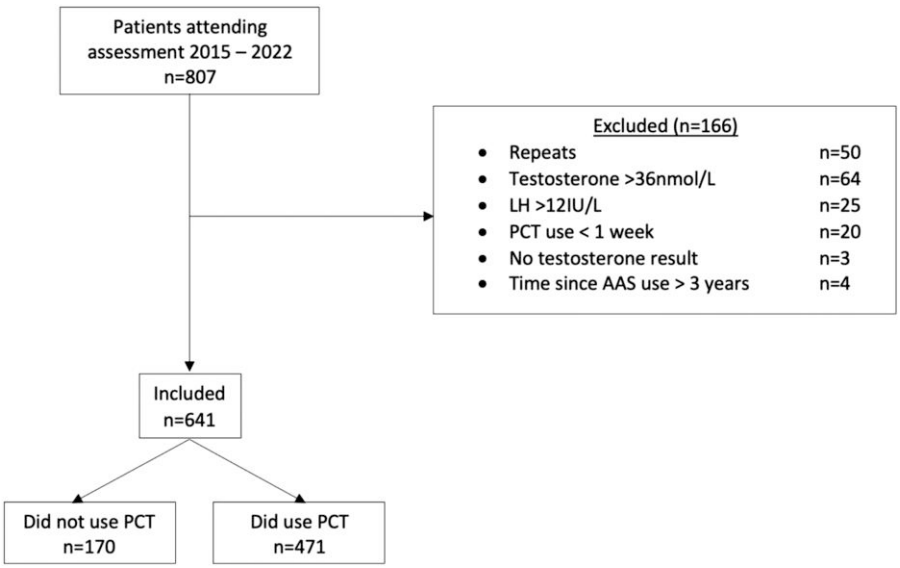

Figure 1. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) flowchart showing the deposition of men using AAS. Men with serum total testosterone and LH above reference range were excluded (Testosterone reference range 10-36 nmol/L, LH reference range 1-12 IU/L). LH, luteinizing hormone; n, number; PCT, post-cycle therapy.

duration ($n = 438$); time since last AAS ($n = 526$); type of AAS used ($n = 528$); use of other image and performance-enhancing drugs ($n = 528$); PCT drugs used ($n = 469$).

Statistical analysis

Data normality was assessed visually with histograms and quantile-quantile plots using SPSS Statistics version 29. Statistical analysis of baseline characteristics was performed using GraphPad Prism version 9. Multivariable analysis was performed using Stata version 15.1. Continuous data is reported as mean ± standard deviation or median with interquartile range as stated. Data was analyzed with an unpaired t-test with Welch's correction for normally distributed data or Mann-Whitney test for non-normally distributed data. Categorical data was reported as numbers and percentages and analyzed using Fisher's exact test.

The primary outcome was a combination of reference range serum levels of all the following, to provide a surrogate marker for biochemical gonadal recovery: LH; FSH; total testosterone. The secondary end point was individual serum levels of LH; FSH; total testosterone. Logistic regression was performed with the primary outcome measured as a binary variable (yes/no). Linear regression was performed for the secondary end point, with individual hormones measured on a continuous scale. LH and FSH had strongly positively skewed distributions and were analyzed on a log scale. All variables possibly related to the outcome were considered independent variables and included in the final regression model; age; number of AAS used; AAS cycle duration; time since last AAS; and use of PCT. Predictor variables with a heavily skewed distribution were divided into categories for the purpose of analysis (AAS cycle duration and time since last AAS). Separately, the interaction between each pair of variables was added to the regression model. If the interaction was significant, it was retained in the model. A P value <.05 was considered statistically significant. Statistical analysis was independently performed by P.B.

Results

Characteristics of men stopping AAS with PCT or without PCT

The characteristics of men attending clinic within 3 years after AAS cessation without PCT (no-PCT group) or with PCT are summarized in Table 1. The PCT group had nonsignificant trends for lower mean age (years: 32.8 ± 7.6, PCT; 34.5 ± 9.4, no-PCT; $P = .07$), longer median AAS cycle duration (weeks: 13.0 (interquartile range (IQR) 10.0-19.75), PCT; 12.0 (7.0-26.0), no-PCT; $P = .29$), and shorter time since last AAS use (weeks: 10.0 (8.0-17.0), PCT; 13.0 (5.0-30.0), no-PCT; $P = .11$) compared with no-PCT. A combination regime of testosterone, dihydrotestosterone (DHT), and 19-Nortestosterone-based AAS ($P = .0404$) was more commonly reported in the PCT than in no-PCT group. Testosterone ($P < .001$), trenbolone ($P = .0472$), drostanolone ($P = .0159$), boldenone ($P = .0426$), and mesterolone ($P = .0430$) use were more frequently reported in the PCT group than non-PCT group. DHT-based AAS ($P < .001$) and oxandrolone ($P = .0386$) were more frequently reported to be used by the no-PCT group. Several combinations of PCT were reported by users. Most men had taken tamoxifen (75%), clomiphene (77%), or hCG (74%) alone or in combination for PCT. Anastrazole was self-reported by 4% of men (Table 1).

Comparison of normalization of reproductive hormones between PCT and no-PCT groups

We then analyzed which participants attending the clinic had evidence of normalization of reproductive hormones from post-AAS hypogonadism ie, a combination of a reference range serum level of all the following: LH; FSH; total testosterone. Each patient had a random, non-fasted blood sample taken between 1 week and 36 months following the last reported consumption of AAS.

Normalization of reproductive hormones was achieved in 48.2% of men (309/641). PCT use was nonsignificantly associated with a higher likelihood of biochemical recovery

Table 1. Baseline characteristics of men not using and using PCT.

	No-PCT $n = 170$	PCT $n = 471$	*P* value
Age (Mean ± SD)	34.5 ± 9.4	32.8 ± 7.6	.07
AAS cycle duration (weeks) (Median (IQR))	12.0 (7.0-26.0)	13.0 (10.0-19.75)	.29
Time since last AAS use (weeks) (Median (IQR))	13.0 (5.0-30.0)	10.0 (8.0-17.0)	.11
Class of AAS (*n* (%))			
Testosterone based only	50 (37)	120 (30.5)	.1668
DHT based only	13 (9.6)	9 (2.3)	<.001
19-Nortestosterone derivatives only	1 (0.7)	2 (0.5)	>.99
Testosterone based + DHT based	12 (8.9)	46 (11.7)	.4272
Testosterone based + 19-Nortestosterone	41 (30.4)	134 (34.1)	.4593
DHT + 19-Nortestosterone	1 (0.7)	1 (0.3)	.4464
Test + DHT + 19-Nortestosterone	17 (12.6)	81 (20.6)	.0404
Type of AAS (*n* (%))			
Testosterone	115 (86)	380 (96)	<.001
Trenbolone	38 (28)	151 (38)	.0472
Drostanolone	9 (7)	58 (15)	.0159
Boldenone	9 (7)	53 (13)	.0426
Nandrolone	24 (18)	88 (22)	.3281
Stanozolol	3 (2)	27 (7)	.0513
Methandienone	11 (8)	42 (11)	.5065
Mesterolone	0	12 (3)	.0430
Oxandrolone	29 (22)	54 (14)	.0386
Metenolone	1 (0.7)	10 (2)	0.3049
Oxymetholone	6 (4)	20 (5)	>.99
Other drugs during cycle (*n* (%))			
hCG	1 (0.7)	5 (1)	>.99
Insulin	0	2 (0.5)	>.99
Clenbuterol	3 (2)	5 (1)	.4248
Growth hormone	6 (4)	13 (3)	.5913
Drugs as PCT (*n* (%))			
Tamoxifen	0	352 (75)	
Clomiphene	0	362 (77)	
Human chorionic gonadotrophin (hCG)	0	347 (74)	
Tamoxifen + Clomiphene + hCG	0	222 (47)	
Anastrazole	0	18 (4)	

Abbreviations: AAS, anabolic-androgenic steroids; DHT, dihydrotestosterone; hCG, human chorionic gonadotrophin; IQR, interquartile range; *n*, number; PCT, post-cycle therapy; Test, testosterone.

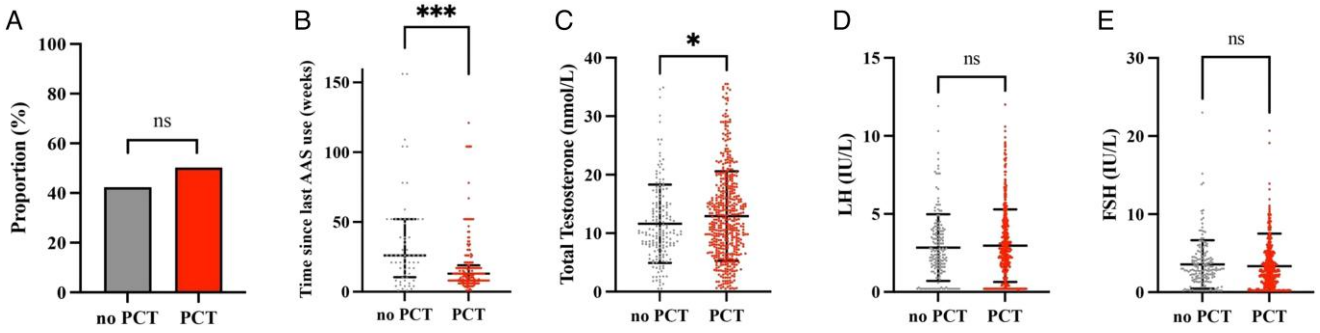

Figure 2. Normalization of reproductive hormones and individual serum reproductive hormones in men not using and using PCT. Separate plots are shown for the entire cohort. (A) Proportion of men (%) with normalization of reproductive hormones, (B) time since last reported AAS use (weeks) presented as median with interquartile range in men with normalization of reproductive hormones, (C) total testosterone (nmol/L) presented as mean and standard deviation, (D) LH (IU/L) presented as mean and standard deviation, (E) FSH (IU/L) presented as mean and standard deviation. AAS, anabolic-androgenic steroids; FSH, Follicle stimulating hormone; LH, luteinizing hormone; PCT, post-cycle therapy. **P* value ≤.05, ****P* value ≤.001, ns, nonsignificant.

following AAS cessation (72/170, 42%, no-PCT; 237/471, 50%, PCT; $P = .08$; Figure 2A). Furthermore, biochemical recovery was achieved more quickly in men who had taken PCT compared with those who had not taken PCT (time since last reported AAS in weeks: 26.0 (IQR 10.5-52), no-PCT; 13.0 (IQR 8.0-19.0), PCT; $P < .001$; Figure 2B). Men in the PCT group had a trend to be younger and have a shorter interval since AAS cessation. We therefore conducted a multivariable regression to investigate factors associated with biochemical recovery from AAS use (Table 2).

Table 2. Multivariable associations with normalization of reproductive hormones.

Variable	Subgroup	Category	Odds ratio (95% CI)	*P* value
Age[a]	—	—	0.93 (0.69, 1.24)	.60
Use of PCT	Last AAS use ≤3 months	No	1	.001
		Yes	3.80 (1.78, 8.10)	
	Last AAS use >3 months	No	1	.99
		Yes	1.01 (0.47, 2.17)	
Number of AAS	—	1	1	.009
		2	0.55 (0.31, 0.98)	
		3	0.46 (0.24, 0.88)	
		4+	0.25 (0.11, 0.58)	
AAS cycle duration	—	≤3 months	1	.01
		3-6 months	0.76 (0.46, 1.25)	
		>6 months	0.34 (0.17, 0.70)	
Time since last AAS use	No PCT use	≤3 months	1	<.001
		>3 months	5.68 (2.26, 14.2)	
	PCT use	≤3 months	1	.13
		>3 months	1.50 (0.88, 10.9)	

Multivariable associations of variables and interactions (subgroup) with normalization of reproductive hormones are defined as a combination of a reference range serum level of all the following: total testosterone; LH; FSH.
Abbreviations: AAS, anabolic-androgenic steroids; CI, confidence interval; FSH, Follicle stimulating hormone; LH, luteinizing hormone; PCT, post-cycle therapy.
[a]Odds ratio given for a 10-year increase in age.

Multivariable analysis

The analysis results suggested a significant interaction between PCT use and time since last AAS ($P = .01$), but no significant interaction between any other variables. Therefore, associations with PCT were subdivided into men self-reporting AAS cessation ≤3 or >3 months previously.

PCT was associated with an increased probability of gonadal hormonal normalization in men stopping AAS within 3 months (odds ratio [OR] for normalization compared with no-PCT with last AAS ≤3 months: 3.80, 95% CI [1.78, 8.10]; $P = .001$). There was no significant effect of PCT in men last using AAS greater than 3 months previously (odds ratio for normalization compared with no-PCT with last AAS >3 months: 1.01 [0.47, 2.17]; $P = .99$). Men using a greater number of AAS drugs had a poorer prognosis of gonadal normalization compared with men using a single AAS drug (odds ratio for normalization compared with a single drug: 2 OR 0.55, 95% CI [0.31, 0.98]; 3 OR 0.46, 95% CI [0.24, 0.88]; 4 or more OR 0.25, 95% CI [0.11, 0.58]; $P = .009$. The prognosis for gonadal hormonal normalization was lower with longer AAS cycle duration (odds ratio for normalization compared with ≤3 months: 3-6 months OR 0.76, 95% CI [0.46, 1.25]; >6 months OR 0.34, 95% CI [0.17, 0.70]; $P = .01$). As expected, the prognosis for gonadal hormonal normalization was higher with a longer time-period since last AAS with no PCT use (odds ratio for normalization for >3 months compared with ≤3 months with no PCT use: 5.68, 95% CI [2.26, 14.2]; $P < .001$). However, the time since last AAS use was not significantly associated with normalization of reproductive hormones if men had also reported PCT use (odds ratio for normalization for >3 months compared with ≤3 months with PCT use: 1.50, 95% CI [0.88, 10.9]; $P = .13$).

Comparison of individual serum reproductive hormones between PCT and no-PCT groups

PCT use was associated with higher serum total testosterone levels following AAS cessation (mean total testosterone nmol/L: 11.6 ± 6.7, no-PCT; 12.9 ± 7.7, PCT; $P = .0346$; Figure 2C). Mean LH values (mean LH IU/L: 2.85 ± 2.14, no-PCT; 2.97 ± 2.32, PCT; $P = .5249$; Figure 2D) and mean FSH values were similar between both groups (mean FSH IU/L: 3.55 ± 3.10, no-PCT; 3.34 ± 4.18, PCT; $P = .4851$; Figure 2E). There were no significant correlations between serum total testosterone, LH, and FSH and time since last reported AAS in both the PCT and no-PCT groups.

Multivariable analysis

We further explored the relationships between PCT use and levels of individual serum reproductive hormones in men who recently stopping AAS (Table 3). As observed with overall biochemical recovery, associations of PCT with individual reproductive hormone levels interacted significantly with time since last reported AAS (total testosterone, $P = .04$); serum LH, $P = .01$; serum FSH, $P = .03$). Therefore, associations with PCT were subdivided into men self-reporting AAS cessation ≤3 or >3 months previously.

Higher serum total testosterone and LH were significantly associated with PCT use when last AAS was less than 3 months ago ($P = .004$ and $P = .006$, respectively). Self-reporting a greater number of AAS drugs was associated with lower serum LH ($P = .007$) and serum FSH ($P = .008$), but associations with serum testosterone were nonsignificant ($P = .05$). In men not taking PCT, less recent AAS use was associated with significantly higher total testosterone ($P = .02$), serum LH ($P < .001$) and serum FSH (<0.001). In men taking PCT, a longer time-period since last reported AAS was associated with a significantly higher serum FSH ($P = .03$), but neither with LH ($P = .05$) nor testosterone ($P = .84$). Neither AAS cycle duration nor patient age was associated with levels of any measured serum reproductive hormone.

Discussion

It is likely that several millions of men worldwide are using AAS illicitly, but there is no recommended therapeutic approach to support AAS cessation. PCT is commonly taken illicitly by men in the hope of improving testicular recovery following AAS withdrawal. However, PCT, like AAS, is a heterogenous group of illicit drugs, which may further

Table 3. Multivariable associations with total testosterone, LH, and FSH.

Variable	Subgroup	Category	Parameter	Coefficient (95% CI)	*P* value
Age[a]	—	—	Total testosterone	−1.0 (−2.0, 1.24)	.05
			LH	0.95 (0.82, 1.11)	.53
			FSH	1.08 (0.93, 1.25)	.30
Use of PCT	Last AAS use ≤3 months	No	Total testosterone	0	.004
			LH	1	.006
			FSH	1	.08
		Yes	Total testosterone	3.5 (1.2, 5.9)	
			LH	1.66 (1.16, 2.37)	
			FSH	1.24 (0.96, 1.94)	
	Last AAS use >3 months	No	Total testosterone	0	.92
			LH	1	.42
			FSH	1	.17
		Yes	Total testosterone	−0.1 (−2.8, 2.5)	
			LH	0.85 (0.56, 1.27)	
			FSH	0.76 (0.51, 1.13)	
Number of AAS	—	1	Total testosterone	0	.05
			LH	1	.007
			FSH	1	.008
		2	Total testosterone	−0.6 (−2.6, 1.3)	
			LH	0.73 (0.54, 0.98)	
			FSH	0.76 (0.57, 1.02)	
		3	Total testosterone	−2.5 (0.24, −0.2)	
			LH	0.64 (0.46, 0.91)	
			FSH	0.64 (0.46, 0.89)	
		4+	Total testosterone	−3.2 (−6.0, −0.5)	
			LH	0.50 (0.33, 0.77)	
			FSH	0.52 (0.34, 0.78)	
AAS cycle duration	—	≤3 months	Total testosterone	0	.05
			LH	1	.43
			FSH	1	.57
		3-6 months	Total testosterone	0.5 (−1.3, 2.2)	
			LH	0.85 (0.66, 1.11)	
			FSH	0.87 (0.67, 1.36)	
		>6 months	Total testosterone	−2.4 (−4.8, −0.1)	
			LH	0.85 (0.59, 2.21)	
			FSH	0.96 (0.68, 1.36)	
Time since last AAS use	No PCT use	≤3 months	Total testosterone	0	.02
			LH	1	<.001
			FSH	1	<.001
		>3 months	Total testosterone	3.5 (0.5, 6.5)	
			LH	2.60 (1.65, 4.08)	
			FSH	2.68 (1.72, 4.17)	
	PCT use	≤3 months	Total testosterone	0	.84
			LH	1	.05
			FSH	1	.03
		>3 months	Total testosterone	−0.1 (−2.1, 1.7)	
			LH	1.32 (1.00, 1.76)	
			FSH	1.49 (1.13, 1.96)	

Multivariable associations of variables and interactions (subgroup) with total testosterone, LH, and FSH. Total testosterone is reported as regression coefficient with confidence intervals. LH and FSH are given as ratios with confidence intervals.
Abbreviations: AAS, anabolic-androgenic steroids; CI, Confidence interval; FSH, Follicle stimulating hormone; LH, luteinizing hormone; PCT, Post-cycle therapy.
[a]Regression coefficient given for 10-year increase in age.

detrimentally affect reproductive recovery. We have conducted the largest-ever study of men stopping AAS with or without illicit PCT. Less than half of men had fully recovered testicular biochemical function at the time of testing. Furthermore, recent PCT use was independently associated with a nearly 4-fold higher chance of normalized reproductive hormones, a surrogate marker of gonadal recovery, following AAS. The unexpected findings of this retrospective study require careful interpretation but warrant further investigation of the therapeutic potential for PCT to modulate AAS withdrawal.

Three recent studies have suggested that serum testosterone or gonadotrophins are lower than normal in men following AAS. Kanayama et al. observed that men with confirmed AAS cessation for either 3 or 6 months had lower testosterone levels compared to nonusers.[11] Rasmussen et al. reported that 27.2% of men without self-reported AAS for at least 6 months were below the lower reference limit for plasma total testosterone and had normal levels of SHBG (which may be suppressed during AAS).[12] Furthermore, Shankara-Narayana et al. observed that serum levels of gonadotrophins were lower in past-AAS users compared with nonusers.[2] Our findings showed that only 48.2% of men had achieved normalization of reproductive hormones after cessation of AAS. In summary, there appears limited evidence suggesting that recovery of physiological

reproductive hormone secretion may not immediately accompany clearance of exogenous AAS from the body.

PCT typically comprises of hCG and SERMs which directly and indirectly stimulate testosterone secretion respectively. hCG has been reported to restore spermatogenesis and testosterone levels in case studies of men following AAS use.[28,31,32] Furthermore, a retrospective study of hCG with supplemental therapy (clomiphene, tamoxifen, anastrazole) suggested its potential feasibility for treating men with exogenous testosterone-related infertility, including previous AAS use.[24] However, hCG monotherapy would be predicted to hinder recovery from exogenous AAS, by perpetuating suppression of endogenous GnRH/LH secretion. Some men take PCT comprising both hCG and SERM for 1-3 weeks, which is followed by SERM monotherapy.[21,33] The aim of such an empirical, unproven protocol is to gain symptomatic benefit by directly stimulating testosterone secretion (using hCG) in the first few weeks after AAS cessation when SERMs would be predicted to be least effective (ie, when serum GnRH/LH/FSH are lowest immediately following AAS cessation). SERMS would not be predicted to stimulate testicular function if serum gonadotrophin levels were completely suppressed. However, most men in our study had detectable serum LH and FSH levels within 1 month of reporting AAS cessation.

Two recent studies have analyzed potential associations between PCT use and recovery from post-AAS hypogonadism. Shankara-Narayana et al. conducted a cross-sectional, observational study of 41 current users, 31 past-users, and 21 non-users in Australia; the number of participants taking substances frequently used as PCT was similar to what we have reported, but no association with PCT use was observed.[2] Smit et al. conducted an observational study of recovery from post-AAS hypogonadism in 100 male athletes within the Netherlands. They reported no difference in total testosterone or LH levels 3 months after an AAS cycle compared to baseline. While no association with PCT use was reported, few participants (20 men) did not use PCT, which may have limited their analysis.[14] Unlike these 2 prior studies, we observed a higher probability of gonadal hormonal normalization in men taking PCT within the first 3 months of AAS cessation. Clinical characteristics of our study were broadly similar to studies by Shankara-Narayana et al. and Smit et al.; the most common age group was 20-39 years, and a wide variety and combination of AAS types were reported by participants.[2,14,27] Furthermore, we reported PCT usage in 76% of men stopping AAS, which corresponds closely with Smit et al.[14,27] The large size of our study (size 3-fold larger) compared with these prior studies combined, may have enabled us to identify a true, previously unidentified, association of PCT with improved recovery from post-AAS hypogonadism. It remains possible that geographical factors may have altered the characteristics of PCT drug products taken by users or other use behaviors in our UK study, compared with the other studies. Finally, it is also important to consider PCT regimes self-administered by men were neither standardized nor validated, and we cannot exclude that other, unidentified confounding factors accounted for the observed associations. Furthermore, it is premature (and inappropriate) to imply that any regimen of PCT could improve recovery from post-AAS hypogonadism. Appropriately designed studies would be needed to further explore the potential for PCT to modify testicular recovery in the short-term within a harm reduction program following AAS cessation.

Identifying other factors associated with recovery from post-AAS hypogonadism may help educate users to avoid the highest-risk patterns of AAS use. A prior Russian uncontrolled study of 44 men reported significant correlations between serum testosterone levels and the duration, dose, and numbers of AAS drugs reported.[34] Other studies however have reported no significant association between age, time since cessation, cycle duration, cumulative life-time AAS, and number of AAS types used with gonadal recovery.[2,11,12,14] Our study highlighted a 4-fold higher likelihood of gonadal hormonal normalization from hypogonadism when men reported using a single AAS drug compared with 4 separate AAS drugs. We also observed that men using AAS for under 3 months duration, had a 3-fold higher chance of gonadal hormonal normalization compared with men using AAS for over 6 months. Similarly, in men last reporting AAS consumption over 3 months ago, they had a 5-fold higher chance of gonadal hormonal normalization compared with men reporting AAS consumption within the last 3 months when PCT was not used. When PCT was used, the association between recovery and greater time since AAS was no longer significant. Other studies have reported a highly variable duration of hypogonadism following AAS cessation.[2,11,13,14,34] Male contraceptives trials and testosterone trials in eugonadal men have suggested that most men recover reproductive function within 12 months following treatment cessation, however longer durations of AAS exposure may prolong the time to recovery.[35] Our univariate analysis did not show a significant correlation between time since last reported AAS and individual hormones (total testosterone, LH, and FSH) in the groups using and not using PCT (Figure S1). In contrast, Shankara-Narayana et al. however, showed a positive correlation between time since last use (days) against serum LH and FSH.[2] The mechanisms of protracted recovery following AAS exposure may involve suppression of hypothalamic kisspeptin expression, needed for GnRH, and desensitization of GABAergic receptors on GnRH neurons, however, these are yet to be fully established.[36,37] Our study provides data quantifying the strength of different interactions. Future, larger-scale studies could be used to build risk-models identify users most likely to need medical support during AAS withdrawal to prevent relapse.

Limitations

This study's large size compared with prior publications permitted multivariable analysis to determine factors associated with gonadal recovery. Furthermore, it summarizes clinical experience within a harm reduction service supporting men stopping AAS. However, it is important to fully consider the limitations of this study. This was an observational study of a convenience-based sample in which blood was drawn at widely varying intervals after steroid use. The use of AAS and the follow-up is subject to recall bias, the exact dose and composition of illicit AAS are largely unknown, and there is potential indication bias (for the use of PCT) and selection bias. The PCT and non-PCT groups were not matched so were different for many parameters, although this may have been mitigated by multivariable analysis. The duration, dose, and timing of PCT relative to the steroid regimen were highly variable and is not described. Tests for nondisclosed AAS use were not conducted. No information was collected on AAS cycles prior to the ones that users were ceasing at the time of their visit. Men using AAS may have other

substance use disorders; we had no information about concomitant opioid use, which is known to cause hypogonadism.[26,38] We were unable to verify the provenance of illicitly purchased PCT, some of which may not have contained any active hCG, SERM, or AI drug product.[39] For this reason, the merit of studying doses of illicitly procured drugs may be limited. Fasting increases serum testosterone, and serum LH is not changed significantly during food ingestion.[40,41] Therefore, the use of nonfasting samples may have enhanced the specificity of classifying men as having "biochemical gonadal recovery"; however, this would have also reduced the sensitivity of detecting "biochemical gonadal recovery". Serum total testosterone was determined using validated immunoassay. Mass spectrometry may be superior to immunoassay at low levels of serum total testosterone however our primary outcome only required determination if serum testosterone levels were within the adult male reference range (10-36 nmol/L); the accuracy at low levels of serum total testosterone is unlikely to have changed our conclusion. Our use of a joint endpoint to define normalization of gonadal hormones, attempted to identify concurrent AAS or PCT use; specifically, elevated LH/FSH suggests current SERM exposure, low LH/FSH with raised testosterone suggests current testosterone-based AAS exposure, and low LH/FSH with low testosterone suggest either current nontestosterone AAS exposure or post-AAS hypogonadism. In keeping with our study criteria, low serum LH has been recently been shown to correlate with concealed AAS use detected on urine toxicology analysis.[42] We also excluded anyone self-reporting AAS or PCT use within the last 1 week. However, it is important to consider whether individuals with hormone levels in the reference range can be considered "recovered". The lack of contemporaneous toxicological AAS testing means we cannot exclude that some men had residual amounts of PCT in their circulations, which may have artificially increased testosterone to within reference levels; if reference range LH and FSH levels were also present, then the end-point of "biochemical recovery" would have been achieved, but it we would expect endogenous testosterone levels to quickly once PCT-induced testosterone secretion stopped. We therefore cannot exclude that recovery appeared quicker in the PCT group since some men had residual, circulating PCT during the blood test. Consistent with this observation, recovery levels were equally low in both groups 3 months after last AAS use, when it can be assumed that none of the participants were still using PCT. It is therefore premature to interpret our study as evidence that PCT encourages hypothalamic-pituitary-gonadal axis recovery in men stopping AAS, although this is possible.

Conclusion

In summary, this study of real-world practice suggests several factors associated with an altered chance of normalization of reproductive hormones and recovery from post-AAS hypogonadism. Men should be advised that fewer AAS drugs used and AAS usage under 3 months are associated with endocrine recovery following their cessation. PCT remains an ill-defined and illicit drug category, but their association with normalized reproductive hormones following recent AAS use raises the important question whether they have future therapeutic potential. Interventional studies are therefore warranted to determine the effects of PCT on endocrine recovery in men following AAS cessation.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Authors' contributions

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Data availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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