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CASE REPORT

Conservative management of azoospermia following steroid abuse

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As well as athletes and competitive body builders, recreational body builders attending gymnasia are known to abuse anabolic steroids, using doses from 10- to 40-fold above physiological levels. Androgenic steroids induce hypogonadotrophic hypogonadism with associated azoospermia, leading to infertility. Little literature exists on the treatment of steroid-induced azoospermia following the cessation of abuse. We present four cases of steroid-induced azoospermia, its conservative management and eventual return of normal semen density.

Key words: abuse/azoospermia/infertility/steroid

Introduction

Anabolic steroids have been used by athletes to improve strength and performance for more than 40 years (Lukas, 1993). Abuse by competitive body builders is thought to be common, but recreational body builders attending gymnasia also abuse steroids (Perry *et al*., 1992). In these settings, high doses from 10- to 40-fold above physiological levels are being used (Kilshaw *et al*., 1975; Knuth *et al*., 1989).

Among well-reported side-effects, androgenic steroids also induce hypogonadotrophic hypogonadism with associated azoospermia (Schurmeyer *et al*., 1984). Hence, users of anabolic steroids often seek medical attention because of infertility (Kilshaw *et al*., 1975). However, little literature exists on the treatment of steroid-induced infertility and the duration of azoospermia following the cessation of abuse.

We present four cases of steroid-induced azoospermia which returned to normal spontaneously, following cessation of steroid abuse, with pregnancies occurring in at least three of the cases. All patients were questioned in detail concerning the type, dosage and frequency of drug taking. However, it was apparent that the patients were reluctant to give a detailed account and it was impossible to be certain as to the accuracy of their histories.

Case 1

A 31 year old man was referred to the regional andrology clinic with a 6 year history of secondary infertility due to azoospermia. He was an amateur body builder and had been taking 8 week courses of steroids during the last 5 years. On examination testicular volume was found to be reduced to 15 ml. Seminal analysis confirmed azoospermia. Serum follicle stimulating hormone (FSH) values were 0.6 U/l (2.0–8.0) and luteinizing hormone (LH) values were 2.8 U/l (2.0–10.0). Serum testosterone concentrations were 3.7 nmol/l (9.0–40.0 nmol/l). The patient was advised to discontinue steroids.

One year following the cessation of steroid abuse there was some improvement in conventional seminal parameters. Sperm concentration was 17×10^6/ml, with 20% progressive motility and 25% flagellate motility. Similarly pituitary gonadotrophins: were FSH 2.1 U/l, LH 3.9 U/l and testosterone 7.3 nmol/l.

Eighteen months into the cessation of steroid abuse the sperm concentration was 112 $\times10^6$/ml with 47% progressive motility and 5% flagellate motility. The FSH was 2.6 U/l, LH 5.1 U/l and testosterone 6.6 nmol/l. The couple achieved a pregnancy spontaneously 20 months after cessation of steroid abuse.

Case 2

A 33 year old man was referred to the regional andrology unit for consideration for treatment with donor semen following a diagnosis of primary infertility due to azoospermia. He was a keen body builder and was using steroids. The testicular volume was reduced to 12 ml. His endocrine profile on presentation was FSH 0.6 U/l, LH 1.8 U/l, testosterone 24.6 nmol/l, and the semen analysis confirmed azoospermia.

He was counselled as to the avoidance of steroids and within the first 6 months of abstinence the sperm concentration was 7.4 $\times10^6$/ml with 35% progressive motility and 7% flagellate motility. His FSH was 1.9 U/l, LH 4.3 U/l and testosterone 1.3 nmol/l. Eight months into the conservative management the sperm concentration had improved to 32.9 $\times10^6$/ml, 56% progressive motility and 26% flagellate motility. The FSH was 2.3 U/l, LH 3.7 U/l, testosterone 11.2 nmol/l and the testicular volume 18 ml. Despite the improvement of semen parameters the patient did not attend any further clinic appointments. He was later found to have returned to steroid abuse.

Case 3

A couple (husband aged 27 years) was referred to the clinic with primary infertility of 3 years. Initial investigations had

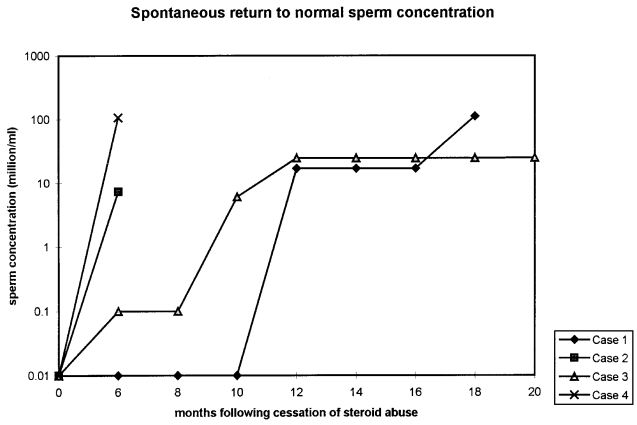

Figure 1. The spontaneous return of sperm concentration to normal values during abstinence from steroid abuse.

shown azoospermia. He was a body builder and had been abusing steroids. He was advised accordingly regarding the abuse of steroids. A repeat semen analysis after 6 months abstinence from steroids showed a sperm concentration of 1×10^5/ml with 30% progressive motility and 60% flagellate motility. He was then referred to the regional andrology clinic. On examination testicular volume was normal (20 ml), FSH was 1.9 U/l, LH 4.6 U/l. Testosterone values were not measured due to the small volume of blood available. Five months later the sperm concentration was 6.1×10^6/ml with 35% progressive motility and 30% flagellate motility. Thirteen months after the cessation of steroid use the sperm concentration was 24.8×10^6/ml with a progressive motility of 25% and flagellate motility of 15%. After 20 months of abstinence the sperm concentration was 25×10^6/ml with a 55% progressive motility and 16% flagellate motility. Two months later, 22 months after discontinuing steroids, the couple achieved a pregnancy.

Case 4

A 28 year old man was referred with 1 year of primary infertility due to azoospermia. He was a body builder and had been abusing steroids for over 4 years. On examination testicular volume was reduced to 14 ml. On the first investigation azoospermia was confirmed alongside suppressed gonadotrophin levels: FSH 0.7 U/l and LH 1.2 U/l. Testosterone concentration was 4.2 nmol/l. Five months after abstinence, his FSH was 0.9 U/l, LH 1.5 U/l, testosterone 6.1 nmol/l and sperm concentration 51.1×10^6/ml with 38% progressive motility and 48% flagellate motility. Testicular volume was normal (20 ml) at that time. A month later the FSH was 0.9 U/l, LH 1.5 U/l, testosterone 11.2 nmol/l, and sperm concentration 106×10^6/ml with 31% progressive motility and 50% flagellate motility. The couple achieved a pregnancy by the ninth month following the cessation of steroids.

The improvement in sperm concentration of the four cases is summarized in Figure 1.

Discussion

Steroid abuse by athletes has continued to increase despite the efforts of various sports organizations to curb a practice which had previously been restricted to weight lifters and professional body builders (Buckley *et al*., 1988). Recreational body builders attending gymnasia are also abusing steroids (Perry *et al*., 1992) but the frequency and patterns of use and the associated problems are less well known.

Spermatogenesis is under the control of FSH and LH, whose secretion is regulated by gonadal steroids and possibly inhibin. Administration of anabolic steroids, as derivatives of testosterone, suppresses gonadotrophin secretion. A hypogonadal state can be induced that is characterized by decreased serum gonadotrophins, decreased serum testosterone concentrations (unless exogenous testosterone is being administered at the time of testing), testicular atrophy and impaired spermatogenesis. These effects result from the negative feed-back of androgens on the hypothalamic–pituitary axis and possibly from local suppressive effects of excess androgens on the testis (Kilshaw *et al*., 1975; Holma and Aldercreutz, 1976; Jarow and Lipshultz, 1990).

The patterns of anabolic steroid administration are largely complex and without a standard. It is essentially difficult to obtain information and history from abusers and it is not always reliable. It is estimated that there are more than 45 anabolic steroid compounds available for abuse by athletes, and their use is increasing among male and female adolescents (Lane and Connor, 1994). Frequently oral and parenteral hormones are used in what is referred to as ‘stacking’ in an effort to maximize steroid receptor binding and increase the desired effects (Lukas, 1993). Steroids are usually cycled, or used for 6–12 weeks followed by abstinence for several weeks (Turek *et al*., 1995). Amongst the preparations used are testosterone esters (propionate, phenylpropionate, isocaproate, and decanoate), testosterone oenanthate, nandrolone decanoate, mestanolone (methylandrostanolone) oenthate in i.m. injectable form, and methandienone, oxandrolone and stanozolol in tablet form.

Androgenic steroids are known to cause impaired spermatogenesis (Heller *et al*., 1950) and the use of 19-nortestosterone has even been suggested for male contraception (Schurmeyer *et al*., 1984; Knuth *et al*., 1985). Hormonal suppression of sperm production provides reversible contraception (Wu, 1996). Infertility following anabolic steroid use commonly presents as oligozoospermia or azoospermia along with abnormalities of sperm motility and morphology (Kilshaw *et al*., 1975; Holma, 1977; Knuth *et al*., 1989; Jarow and Lipschultz, 1990). Data available from the development of androgenic steroids for male contraception indicate that reversal of effects can take up to 12 months after discontinuation of the drugs (Schurmeyer *et al*., 1984). However, the doses used by body builders may be up to 40-fold higher than therapeutic doses. Furthermore, the multiple preparations used makes it almost impossible to study the adverse effects of individual drugs (Lloyd *et al*., 1996).

There is little literature and considerable disagreement regarding the management of these cases and the treatment of prolonged azoospermia. In a retrospective, cross-sectional, case–control study (Knuth *et al*., 1989) it was suggested that even after prolonged use of high doses of anabolic steroids, sperm production returns to normal without any active treat-

ment. On the other hand Turek *et al*. (1995) suggested that if the semen parameters and endocrine balance are not restored 6 months after the cessation of steroid use the patients should be treated in a similar manner to that used for the Kallman syndrome, hypophysectomy or other forms of hypogonadotrophic hypogonadism. In these diseases there is a lack of FSH and LH production, and a low serum testosterone concentration similar to the findings in athletes taking anabolic steroids (Holma and Adlercreutz, 1976; Knuth *et al*., 1989). Treatment for virilization in these patients involves weekly doses of i.m. testosterone. However, the induction of spermatogenesis requires treatment with gonadotrophins or gonadotrophin analogues, including intramuscular injections of human chorionic gonadotrophin (HCG) (Martikainen *et al*., 1986; Burris *et al*., 1988; Jarow and Lipshultz, 1990) and human menopausal gonadotrophin (HMG) (Burris *et al*., 1988). Subsequently, spermatogenesis can be maintained by HCG injections alone (Turek *et al*., 1995).

The prolonged suppression of gonadotrophin secretion following steroid abuse is analogous with the prolonged suppression of thyroid stimulating hormone following excessive thyroxine intake and the suppression of ACTH from the adrenal following excess hydrocortisone (glucocorticosteroid) therapy. One could speculate that the hypothalamic controlling peptides not only release pituitary hormones but also have a trophic action on the target cells themselves. The suppression of gonadotrophin releasing hormone (GnRH) by the anabolic steroid abuse, according to this hypothesis, would lead to gonadotroph atrophy in the pituitary. The variable return of pituitary function would therefore depend on the rate of recovery of gonadotroph from the atrophic process. Relatively lower doses of steroids used for contraceptive purposes would not be expected to cause, or to cause less extensive, gonadotroph atrophy, which can explain the shorter recovery time for normal spermatogenesis to return following the cessation of use.

Following discontinuation of steroid abuse and return of normal pituitary function one would not expect the sperm concentration to start improving immediately. Once spermatogenesis is arrested it may take as long as 64 days for spermatozoa to appear in the seminiferous tubules (Hellere and Clermont, 1963) and the duration of transit through the ductular system requires a median of 12 days (range 1–21 days) (Rowley *et al*., 1970).

Patients 1, 3 and 4 achieved a pregnancy at 2, 8 and 4 months respectively, following the return of normal semen parameters (concentration $>20\times10^6$/ml). Variation in the time interval between normal spermatogenesis and conception may be due to subtle differences in both male and female fertility status. Similar differences can be observed in all couples and the diagnosis of subfertility is considered only after 12 months of unprotected, regular intercourse.

Conclusion

In conclusion, our cases demonstrate that there is a tremendous variability in the return of spermatogenesis which is impossible to predict from the number, type or duration of anabolic steroids taken. However, it is apparent that prolonged azoospermia following steroid abuse can be successfully managed by conservative means alone and return of fertility achieved.

The slow recovery of gonadotrophins predicts an eventually successful return of fertility. More aggressive treatment with exogenous gonadotrophins and testosterone may be considered if there is absence of improvement in the sperm parameters for longer than 24 months.

It is, however, of paramount importance that awareness of these side-effects is increased among young men who take anabolic steroids recreationally without knowing the potentially serious consequences.

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