

Male Fertility after Androgenic Steroid Use: How Little We Know

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Androgenic steroid (AS) abuse is often described as a public health menace.¹ The lifetime prevalence of AS abuse worldwide appears to be 1-5% in men, but it is much lower in women.² Studies of AS abuse and their effects are hampered by many factors including small numbers of subjects, reliance on questionnaire surveys (subject to untruthful answers about the use of drugs that are stigmatized and/or illegal) and the lack of longitudinal studies before, during and after abuse of AS. In addition, the high prevalence of concomitant use of tobacco, alcohol, marijuana, opioids and other illicit drugs confounds the attribution of the adverse effects of AS abuse.²⁻⁴

AS abuse suppresses the secretion of luteinizing hormone and follicle stimulating hormone that in turn results in decreased spermatogenesis.^{5,6} Studies of supraphysiological dosages of testosterone (an AS) demonstrate that it provides effective contraception in most healthy men with baseline normal spermatogenesis.⁶ These studies of potential androgen-based male hormone contraceptives have consisted of 1-2 years of therapy, and sperm concentrations return to baseline (normal) in 12-16 months after discontinuation in 95% of healthy men. Many experts have concluded that recovery of spermatogenic function occurs similarly within 1-2 years of the discontinuation of chronic AS abuse. However, there appears to be a delay in spermatogenic recovery with longer duration of androgen abuse and longer-acting formulations of androgens.^{2,7} Thus, some men who abuse AS for many years might take longer than 2 years to recover normal spermatogenesis after discontinuation.²

There are significant areas of uncertainty about the effects of AS on male fertility. Conclusions about the effects of exogenous AS on male fertility have been inferred from a marker of male reproduction function (seminal fluid analysis) and case reports of male infertility associated with AS abuse.^{2,5} However, there are few longitudinal data about effects of dosage, type and duration of AS abuse on the timing of recovery of baseline spermatogenesis, and there are almost no data on the recovery of fecundity and fertility.

In this context, the recent study by Windfield-Mathiasen, et al. is useful.⁸ This group of investigators used data from the publicly funded Anti-Doping Denmark program and the Danish national health registry. Anti-Doping Denmark has an agreement with about 80% of the fitness clubs in the country. Under the terms of this agreement, Anti-Doping Denmark performs targeted testing for AS abuse in club members and trainers who are selected based on body morphology and anonymous tips from whistleblowers.

The investigators used anonymized data from Danish men who failed a urine screening test for AS from 2008-2018 while exercising at a fitness club that participated in the anti-doping program. Failure to pass resulted in a 2-year ban from exercise at any club that participates in the anti-doping program. 545 men had urine samples that indicated exogenous androgen abuse (the primary study group), and 644 refused to be tested (and were presumed to have a positive test). The latter group was analyzed separately as a comparator. The investigators compared the confirmed AS abusers with Danish controls who were matched for age and who were living in Denmark. The primary endpoint was live births in the positive test and control groups. Study participants were “followed” via the Danish health registry database for the 10-year period before and the period after the positive AS test.

The investigators made the following assumptions: 1) the earliest effect of AS on live births is 1 year (based on the time required for a complete cycle of spermatogenesis and for a normal gestation); and 2) the abuse of AS is the sole explanation for any observed change in live birth rate in the 2-year interval around the positive urine test (i.e., the year before and the year after the drug sanction) compared to the two-year interval encompassing the second and third year after the positive urine test. The investigators compared the fertility rate (live births per 100-person years) in 2-year intervals before and after the 2-year interval circumscribing the positive test. Fertility rates were very low in the AS and control groups throughout the study, but the positive test group had significantly lower birth rates in the 2-year interval of 12 months to 36 months before the positive test and the 2-year

interval of 12 months before and after the positive test. The fertility rates did not differ between the two groups during the intervals of greater than 60 months, 60 to 36 months before or during the intervals 12 to 36, 36 to 60 or greater than 60 months after the positive test. The AS group was more than twice as likely as the control group to be diagnosed as infertile (6.6% vs. 3.1%; $P < 0.0001$), but both groups were equally likely to seek assisted reproductive technology for infertility treatment (5.7% v. 5.3%; $P = \text{NS}$).

The study has number of strengths including relatively large numbers of AS abusers and excellent longitudinal follow-up in a comprehensive national health registry database. On the other hand, the study has many significant limitations that characterize most AS research: lack of data on type, dosage, and duration of AS abuse and lack of (longitudinal) data on the health and the fecundity and fertility of female partners, desire and attempts to conceive, male hormonal and sperm parameters and non-AS factors that might affect male fertility. There is also a potential bias in this study because the investigators assumed that the AS users stopped AS use after their positive urine test. It is unclear why or if these men stopped AS use after the positive test; they had the option continuing AS use and going to a Danish fitness club that was not participating in the Anti-Doping Denmark program. Finally, the study's findings are limited by the overall low live child birth rates in the primary and control groups. After nearly a decade of follow-up, ~ 55% of men in both groups were childless. The very low cumulative birth rate in the control group may have masked persistent infertility in the AS group. Paradoxically, for men who wish to avoid, delay or limit the number of children they have, the effects of AS on reproductive function might be considered as a contraceptive benefit and not an adverse effect on fertility.

In summary, the Windfield-Mathiasen study demonstrates that AS abuse is associated with significantly reduced live birth rates during abuse and for at least one year after cessation. Decreased fertility due to AS appears to be reversible for most men with short term abuse ($< 3\text{-}4$ years) within 1-

3 years after cessation. The study does not provide any evidence about the rate or completeness of recovery of fertility in men who abuse high-dosages of AS for longer than 3-4 years.

We need more accurate information about the prevalence of chronic worldwide AS abuse, the effects of dose and duration on outcomes (and not just markers) in human health, and the timing and completeness of reversibility of the effects of long-term AS abuse. Prospective, longitudinal studies in countries with national healthcare systems and registries are a good start. At the moment, we have Aristotelian half-truths about the effects of AS on men. Our ignorance prevents rational approaches to solutions to AS abuse because we have not defined the problem and the long-term consequences.

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