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Clinical Research Article

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Male Fertility Before and After Androgen Abuse

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Abbreviations: IVF, in vitro fertilization; RR, rate ratio; SD, standard deviation.

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Abstract

Purpose: Previous research has found that male users of androgens are diagnosed approximately twice as often with infertility. We therefore set out to investigate the fertility in men using androgens.

Methods: The study included 545 males who tested positive for androgens in an anti-doping test program in Danish fitness centers during the period from January 3, 2006, to March 1, 2018. The confirmed androgen users were matched by birth year with 5450 male controls. We followed this cohort from 10 years prior to testing positive until the end of follow-up in May 2018.

Results: During the 10-year period prior to testing positive, the group of androgen users experienced a 26% lower fertility rate than the controls (rate ratio [RR] 0.74; 95% CI, 0.60-0.90; $P = 0.0028$). However, in the years following the doping sanction, they made a significant catch-up, and at completed follow-up the total fertility rate was only 7% lower than expected (RR 0.93, 95% CI, 0.84-1.03). The prevalence of assisted reproduction was 5.69% in the group of androgen users and 5.28% in the control group ($P = 0.69$).

Conclusion: Androgen use was associated with a temporary decline in fertility and most androgen users achieved parenthood without any help from the health care system. Overall, the fertility rate and the prevalence of assisted reproduction among androgen users were close to those in the background population.

Key Words: anabolic steroids, androgenic anabolic steroids, fertility, infertility, assisted reproduction

Visible muscularity is instinctively perceived as a marker of health and high genetic quality, and women may be naturally attracted to strong and tall men (1). This may explain the relatively high prevalence of illegal androgen use among young men, which is reported to be as high as 6% (2). Androgens accelerate muscle growth, but also disturb the hypothalamic-pituitary-gonadal axis, resulting in low levels of gonadotropins, thus leading to decreased

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endogenous testosterone production and reduced spermatogenesis (3-7). Therefore, while users of androgens may appear attractively healthy, they have an increased probability of reduced reproductive capacity—a phenomenon that was recently named the Mossman-Pacey paradox (8, 9). However, whether the damage to fertility is permanent or is contingent on the continued use of androgens, remains to be determined.

A cross-sectional study by Rasmussen et al measured a lineup of surrogate markers related to reproduction and hypogonadism (4). They found that the levels of inhibin B and anti-Müllerian hormone were significantly suppressed in active users of androgens compared with healthy controls but tended to normalize in former androgen abusers (4). Shankara-Narayana et al found similar results with an almost identical study setup, but they also analyzed the seminal fluids and found that sperm concentration and motility did not differ significantly between past users and healthy controls (10). Furthermore, previous research on hormonal male contraception has shown that spermatogenesis tends to recover 6 to 12 months posttherapy (11). Altogether, this evidence indicates that infertility related to androgen use may be reversible. We therefore set out to investigate the fertility in male androgen users as well as the change in their fertility following a positive test in an anti-doping intervention program.

Material and Methods

Research endpoints

1. To compare the fertility rate in androgen users with that of a cohort of age matched male controls
    a. To estimate the difference in fertility rates between the 2 groups
    b. To estimate the difference in the prevalence of assisted reproduction between the 2 groups
2. To estimate the change in fertility following a positive test in an anti-doping intervention program

Design

Retrospective matched cohort study.

Definitions

Cumulative prevalence was based on observations over the 10 years prior to the index date and until the end of the follow-up period. We defined *assisted reproduction* as treatment at an in vitro fertilization (IVF) clinic or treatment with medication that may improve spermatogenesis (ATC: G03G [includes gonadotropins, human chorionic gonadotropin, and clomiphene]). The fertility rate was calculated on the basis of live births documented in the Danish Medical Birth Registry.

The anti-doping program

Since 2006, it has been a political ambition to create a safe and clean fitness environment in Denmark (12). In Denmark, 342 fitness centers (covering 80% of all fitness center members) collaborate with Anti Doping Denmark, which conducts about 1000 inspections of these centers annually. The doping inspectors have primarily tested persons they suspected of androgens use. Those who tested positive or refused to participate received a 2-year doping sanction, equivalent to a 2-year suspension of membership in the collaborating fitness centers (3).

Androgen user cohort

The cohort of androgen users has been described previously (3, 13). In short, 1219 persons were sanctioned for using androgens during the period from January 3, 2006, to March 1, 2018.[1] Of these, 1189 were Danish male citizens, and 545 were sanctioned because androgen traces were found in the urine sample provided, while the remaining 644 were sanctioned because they refused to deliver a urine sample. Although there is a strong suspicion that those who refused to deliver a urine sample were using androgens, we have chosen to analyze the data from the 2 groups as separate cohorts. Thus, in this paper, we present data from the 545 laboratory-confirmed androgen users. As confirmation of the results from the first cohort, data were reanalyzed in the second cohort of the 644 sanctioned persons refusing to deliver a urine sample. These results are presented as supplementary data (14).

Control cohort

For each androgen user we randomly chose 10 male controls from the general population, matched by age and date. For example, a male androgen user born in 1987 who tested positive on May 6, 2012, would be matched with 10 male control individuals from the same birth cohort alive and living in Denmark at that date.

Registries

All residents in Denmark have a unique personal identification number (CPR) that is used in all contacts with the state and the health care system (15). We cross-referenced the

patients' CPR numbers from our 2 cohorts with data from the Danish Civil Registration System, the Danish National Registry of Patients, the Danish National Prescription Register, the Danish Medical Birth Registry, and the Danish IVF registry (15-19). Patients were followed from 10 years prior to baseline and until May 16, 2018. For a detailed description of these registries, please see the supplementary data (14).

Statistics

Patients were followed from 10 years prior to baseline and until the end of the follow-up period on May 16, 2018. In our calculation of observation time, we accounted for migration in and out of Denmark. The fertility rate was calculated for 7 different time periods (Fig. 1).

When testing for differences in means, we used a *t* test for approximately normally distributed continuous variables. When possible, we assessed the robustness of our conclusions using linear regression models (estimated with ordinary least squares) using heteroskedasticity-robust standard errors. In all cases, our qualitative conclusions were unchanged. When testing for independence between categorical variables, we used a chi-square test.

Regression models

We used a regression discontinuity-inspired design to investigate the effect of androgen use on fertility. Regression discontinuity analysis is a rigorous quasi-experimental method for estimating causal effects of treatments on outcomes, in cases where individuals are quasi-randomly treated (20). Based on the regression discontinuity-inspired design, the purpose of this analysis was to investigate the causal effect of doping cessation on the fertility rate in the Danish males using androgens.

We argue that individuals who were just about to test positive for androgen use and individuals who had just been tested positive, did not differ substantially with respect to their fertility except through the effect of the doping sanction. We therefore restrict the sample to a narrow time window consisting of the 2 years leading up to the positive test (or the corresponding point in time for controls) and the 2 years that followed. Since the duration of spermatogenesis is approximately 3 months and the duration of pregnancy is approximately 9 months (21), we can expect that the earliest signs of cessation of androgen will be detectable after 1 year. We therefore compare the number of live births occurring in the period 1 year prior to doping sanction and until 1 year after doping sanction with the number of births occurring in the period 1 to 3 years following doping sanction. We then estimate the change in fertility that occurred after individuals tested positive and, consequently, likely stopped or reduced their use of androgens. To account for the confounding effects of aging we also investigated the same changes in the control group.

When estimating regression models with count data (ie, the number of children born in a given time period) as the outcome variable, we used a Poisson regression model. Since our data only consisted men and was already matched on age and calendar time, we only included androgen use and functions of time as our explanatory variables. Births and exposure were calculated on a monthly basis. Since, in these cases, each individual entered multiple times (up to 48 times in this 4-year period), we calculated cluster-robust *P* values clustered on the level of the individual. For further details, please see the supplementary data (14).

Replication cohort

The 644 males who were sanctioned because they declined to deliver a urine sample were excluded from the main analysis but were included as a special "replication cohort." There is a substantial suspicion that the persons in the replication cohort were using androgens, since they were informed that refusing to participate in the doping control would lead to a doping sanction; secondly we have previously shown that they present the same socio-demographic profile and prevalence of adverse effects as the cohort of men with laboratory-confirmed androgen abuse (3). The results from the replication cohort are presented in supplementary data (14).

Ethics

All data were anonymized, and we had no access to any data that could identify individuals. The study was approved by the Danish Data Protection Agency (2012-58-0004/BFH-2017–105 / 05949), and the Danish National Board of Health (FSEID-00003570/ FSEID-00004621).

Results

We followed 545 male androgen users and 5450 male controls, from 10 years prior to doping sanction/baseline until May 16, 2018. The average age at the time of doping sanction was 26.2 (standard deviation [SD] 6.3) years, and the average length of follow-up was 17.0 (SD 3.9) years in the androgen user cohort and 16.6 (SD 4.1) years in the control group (the difference in means is statistically significant, $P = 0.03$). For further characteristics, please see Table 1.

During the 10-year period prior to baseline, the androgen users experienced a 26% lower fertility rate compared

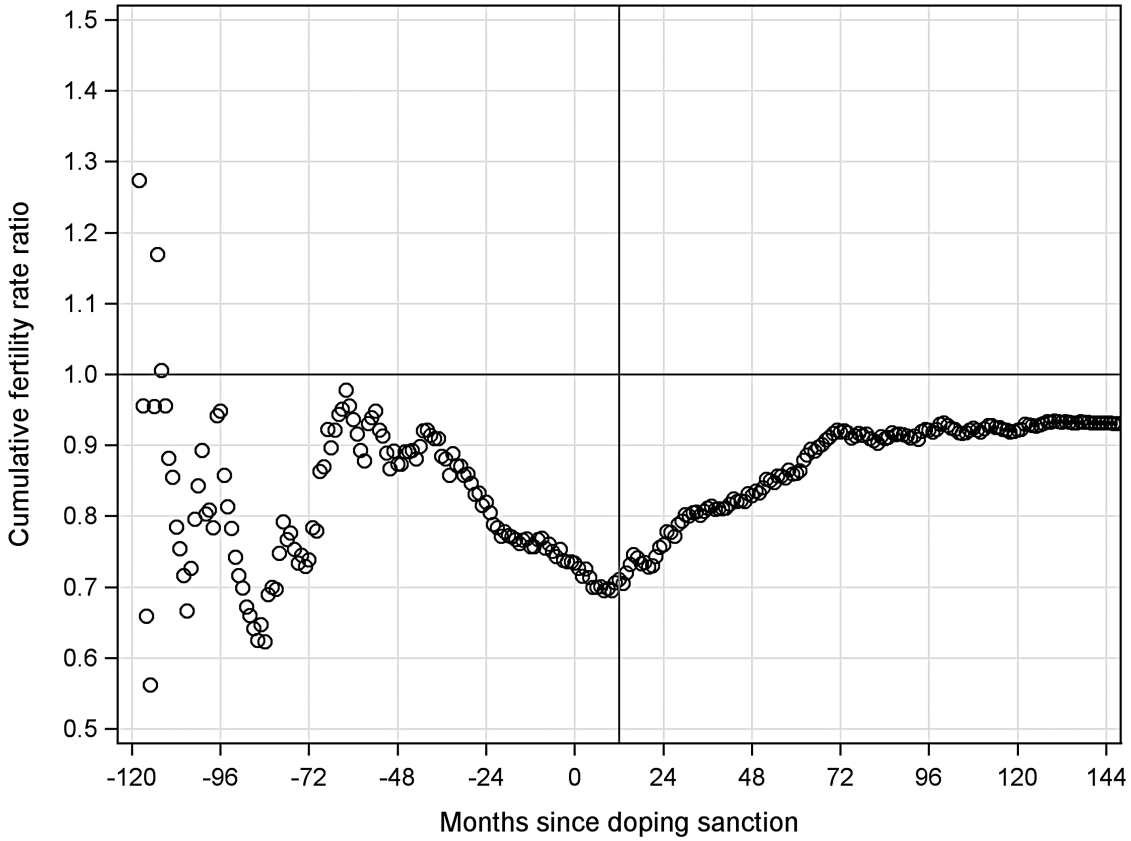

Figure 1. The cumulative fertility rate ratio. Scatter plot of the cumulative fertility rate ratio during the period of investigation. The cumulative fertility rate ratio is calculated as the cumulative fertility rate in the androgen user cohort/ cumulative fertility rate in the control cohort. The cumulative fertility rate ratio seems to reach a local nadir around 1 year after doping sanction at value of 0.70; from there it gradually increases to a value of 0.93 at completed follow-up.

with the matched controls (rate ratio [RR] 0.74; 95% CI, 0.60-0.90; $P = 0.0028$). However, in the years following the doping sanction they made a significant catch-up, and when we completed the follow-up period their fertility rate was only 7% lower than that of the matched controls (RR 0.93; 95% CI, 0.84-1.03). See Table 1 and Fig. 1.

When we completed follow-up, 6.61% of the androgen users had been diagnosed with infertility as opposed to 3.08% among controls ($P < 0.0001$), but our data showed no differences in the frequency of assisted reproduction (Table 1).

Discontinuity analysis

Fig. 2 depicts the development in the fertility rate during the entire period of investigation. Fertility is clearly suppressed in the years prior to doping sanction but then returns to normal in the years following. We now turn our focus to the few years around the doping sanction. Bearing in mind that the average duration of spermatogenesis is 3 months, and the average duration of pregnancy is 9 months, we therefore investigated the changes in fertility that occurred around the balancing point at 12 months after the doping sanction. Fig. 3 depicts the distribution of births from 12 months prior to doping sanction until 36 months after doping sanction. For androgen users the curve is clearly right-skewed.

During this 4-year period, we observed 89 live births among androgen users, 29 occurring from 12 months prior to doping sanction and until 12 months after doping sanction, leading to a fertility rate of 2.73 per 100 person-years, while 60 live births occurred in the second and third years following doping sanction (months 12 to 36), leading to a fertility rate of 6.09 per 100 person-years. Thus, there is a 123% increase in fertility among androgen users during this period. In comparison, there was only a 14% fertility rate increase in the control group during the same time period (Fig. 2). In other words, the increment observed in fertility among androgen users was 95% higher than expected (RR 1.95; 95% CI, 1.23-3.09; $P = 0.0045$).

To more formally assess the effect, we investigated the existence of a discontinuity associated with the doping sanction using a range of Poisson regression models (see supplementary data (14)). Overall, these models establish

Table 1. Summary Statistics

	Baseline			Follow-up		
	Androgen users	Control	*P* value	Androgen Users	Control	*P* value
Age in years (SD)	26.2 (6.3)	26.2 (6.3)	0.99	33.6 (6.4)	33.5 (6.5)	0.74
Person-years	5265	50 975	NA	9276	90 611	NA
Average follow-up in years (SD)	9.7 (1.4)	9.4 (2.1)	0.0007	17.0 (3.9)	16.6 (4.1)	0.03
Number of children	102	1343	NA	382	4008	NA
Fertility rate per 100 person-years	1.94	2.63	0.0028*	4.12	4.42	0.18
Childless	86.24%	83.14%	0.064	54.50%	56.73%	0.31
Assisted reproduction	0.55%	1.41%	0.11	5.69%	5.28%	0.69
Diagnosis of infertility	1.47%	0.94%	0.23	6.61%	3.08%	<0.0001*
No. of observations	545	5450		545	5450	

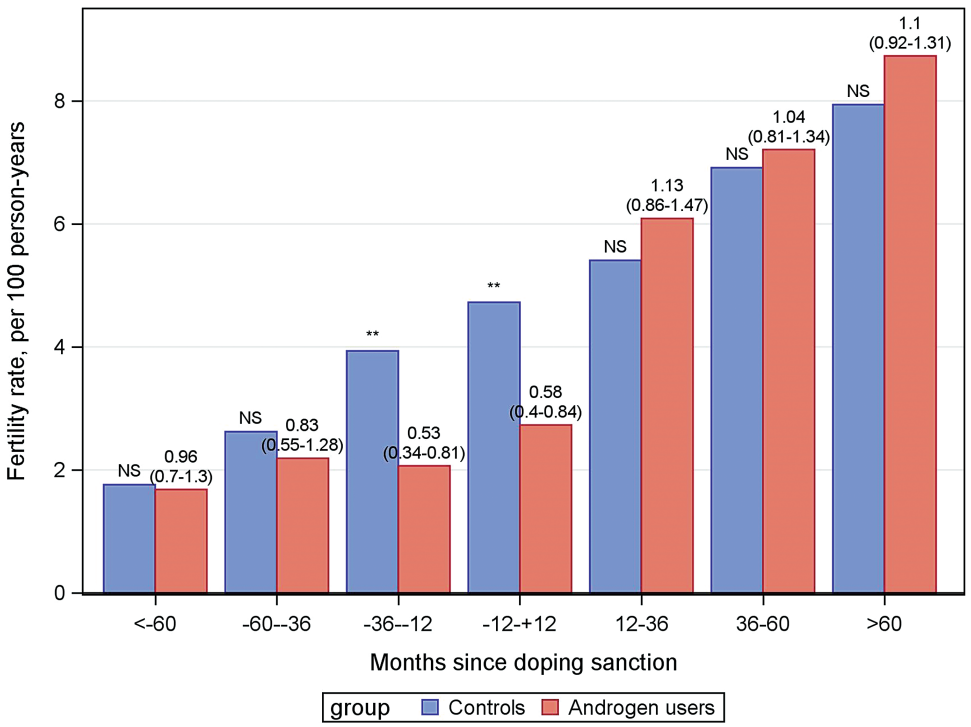

Figure 2. Fertility in male users of androgens and controls. The fertility rate for 7 different time periods. The fertility rate of the men using androgens significantly suppressed compared to the controls in 2 time periods—3 years to 1 year before doping sanction ($P = 0.003$) and 1 year before to 1 year after doping sanction ($P = 0.004$).

a significant positive jump in fertility in the period immediately following the sanction, compared with the period immediately before.

Replication analysis

We analyzed the same parameters in our replication cohort and our estimates were almost identical. However, the fertility rate in this cohort of androgen abusers did not recover fully and ended up 13% lower than the control cohort (RR = 0.87; 95% CI, 0.79-0.97) and the catch-up effect appeared later (Supplementary data (14)).

Discussion

This is the first investigation of the fertility in men abusing androgens. We showed that the fertility rate is significantly lower in the group of androgen users at baseline, but in the

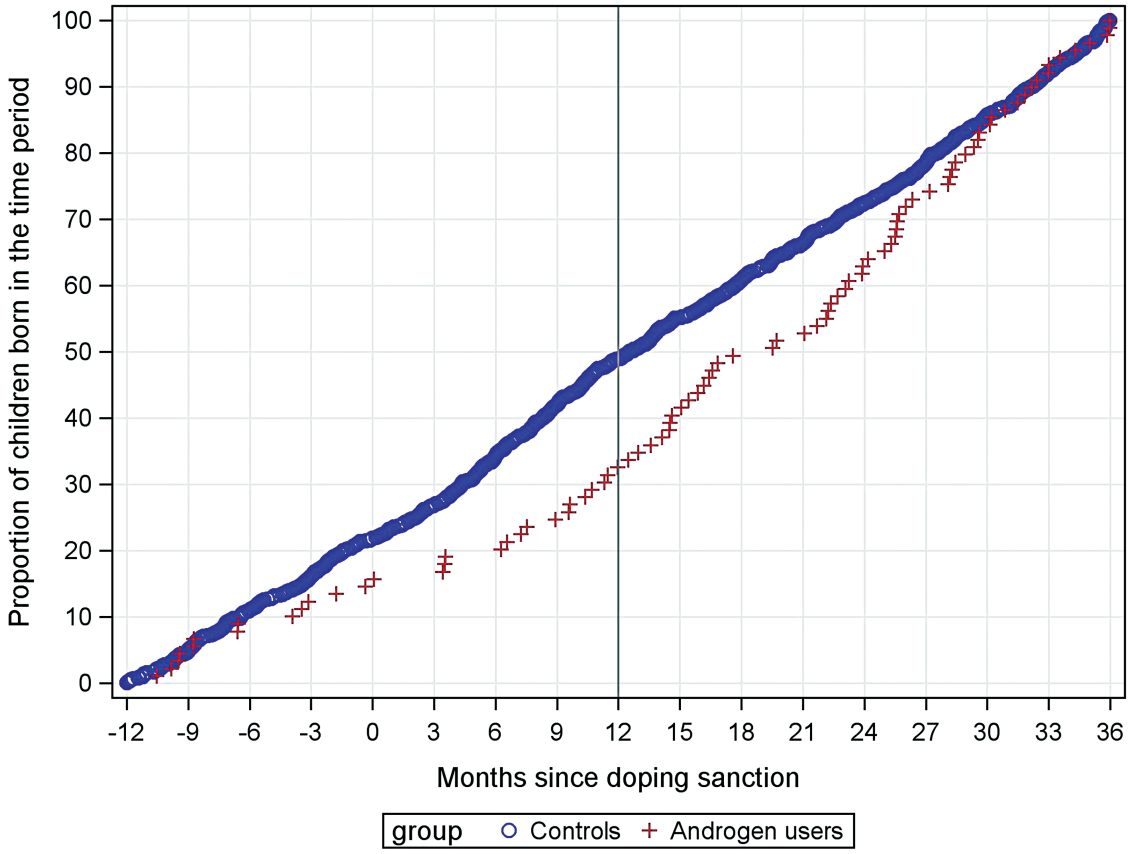

Figure 3. Cumulative distributions of births. The distribution of live births in the period from 1 year prior to doping sanction and until 3 years after doping sanction. The vertical reference line is set at 1 year after doping sanction, since duration of spermatogenesis is approximately 3 months (21) and the duration of pregnancy is approximately 9 months.

years following a doping sanction they seem to catch up. Androgen abuse associated with weightlifting typically involves extensive doses and is known for its broad range of adverse effects, especially hormonal disturbances resulting in gynecomastia, erectile dysfunction, and infertility (8, 22). Consequently, our hypothesis prior to this study was a more irreversible fertility outcome. Interestingly, we found that the prevalence of assisted reproduction was identical with that in the background population. Basically, the fertility rate depends on fecundity and the chances of mating. One may naturally argue that the muscular phenotype associated with androgen use increases the chances of mating; however, if the reproductive capacity was permanently damaged, this would result in low fertility rates and a higher a prevalence of assisted reproduction. In concordance with this, Rasmussen et al and Shankara-Narayana et al found that biomarkers of fertility tended to normalize after cessation of androgen abuse (4, 10). Finally, our results are backed by previous research on hormonal male contraception, which has shown that spermatogenesis tends to fully recover (11).

On a population level, androgen abuse is not expected to have a great impact on the general fertility rate due to the relatively minor prevalence, but the results presented in this study is of importance in the counseling of the individual androgen abuser. Most of these men obtained fatherhood without any assistance from the health care system. Therefore, our data indicate that a "wait-and-see-strategy," in combination with abstinence of androgen abuse, may be a wise first step for the typical androgen user planning parenthood.

Strengths and limitations

Since no other similar studies have been performed, our findings need confirmation in other cohorts. But the fact that we were able to replicate the findings in a replication cohort indicates that the findings are robust. Another major strength of this study is the relatively large cohort of androgen users drawn from Danish fitness centers, rather than from the prison or health care systems, which should reduce selection bias and increase generalizability. Furthermore, high-quality Danish registries enabled us to follow these individuals for an average of 17 years. This allows us to detect the development of fertility several years after a doping sanction.

Retrospective studies have a range of weaknesses, and although we have established that there was a clear improvement in the fertility rate after doping sanction, factors other than the cessation of androgen abuse may have contributed to this finding, for instance, changes in lifestyle, diets, and exercise habits (23, 24). Furthermore, we had no information on sexual activity or relationship status, personal preferences, or life values. Similarly, detailed knowledge about the duration of androgen abuse, preferences for androgen subtypes, and pharmaceuticals bought on the black market, such as clomiphene or human chorionic gonadotropin, would have been preferable (6). A major limitation is the lack of detailed information on physiological markers of fecundity such as sperm count and motility, inhibin B, or anti-Müllerian hormone. Data on assisted reproduction were generated from the Danish National Prescription Register and the Danish IVF registry, which encompass all private and publics hospitals/clinics operating in Denmark and included all types of fertilization procedures. A detailed analysis of the chosen treatment modalities and their success is warranted but given the low prevalence of assisted reproduction in this cohort such data would probably be regarded as disclosive. Finally, it should be noted that the extent to which the assumption that a positive test led to a cessation or a reduction in androgen use cannot be verified. A large fraction of these men probably continued to use androgens; thus, it is more likely we are to *underestimate* the true effect of androgens use on fertility. The estimates presented here can therefore be considered as lower bounds of the true effect.

Conclusion

Androgen use was associated with a temporary decline in fertility and most androgen users obtained parenthood without any help from the health care system. Overall, the fertility rate and the prevalence of assisted reproduction among androgen users were close to that in the background population.

Additional Information

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Data Availability: Restrictions apply to some or all the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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