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# Testosterone use in the male infertility population: prescribing patterns and effects on semen and hormonal parameters

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**Objective:** To analyze how frequently and why men presenting with infertility take testosterone (T) and if negative effects of T on semen parameters are reversed following cessation.
**Design:** Analysis of a prospectively collected database.
**Setting:** Male Infertility clinic.
**Patient(s):** Men presenting for fertility evaluation from 2008 to 2012.
**Intervention(s):** None.
**Main Outcome Measure(s):** The frequency and reason for T use in the infertile male population, and semen and hormonal parameters while on T and following discontinuation.
**Result(s):** A total of 59/4,400 men (1.3%) reported taking T. T was prescribed by a variety of physicians, including endocrinologists (24%), general practitioners (17%), urologists (15%), gynecologists (5%), and reproductive endocrinologists (3%). Only one of the men admitted that he had obtained T from an illicit source. More than 82% of men were prescribed T for the treatment of hypogonadism, but surprisingly, 12% (7/59) were prescribed T to treat their infertility. While on T, 88.4% of men were azoospermic, but by 6 months after T cessation, 65% of the men without other known causes for azoospermia recovered spermatogenesis.
**Conclusion(s):** In Canada, T was not commonly used by men presenting for fertility investigation (1.3%). Close to 2/3 of infertile men using T recovered spermatogenesis within 6 months of T discontinuation. (Fertil Steril® 2013;■:■–■. ©2013 by American Society for Reproductive Medicine.)
**Key Words:** Testosterone, testosterone replacement therapy, male infertility, semen, hormones

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According to Endocrine Society Guidelines, hypogonadal men should be treated with exogenous testosterone (T) when they have consistent signs and symptoms of hypogonadism and low serum T levels (1). Symptomatically, men may report, among other signs, reduced libido, erectile dysfunction, mood changes, irritability, fatigue or memory loss. Asymptomatic men having low serum T may experience decreased bone mineral density (2), decrease in lean body mass and body strength (3), insulin resistance, and adverse cardiovascular consequences (4). According to Endocrine Society guidelines, T replacement therapy is the standard of care for men with symptomatic hypogonadism. In this population, it is an effective, well tolerated, and established treatment.

The side effects of T replacement therapy are relatively well established and include polycythemia, liver dysfunction, adverse lipid profiles, obstructive sleep apnea, and a theoretical increase in prostate cancer risk (1). Exogenous T also impairs sperm production, an effect that not all physicians are aware of. In fertile men, exogenous

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T negatively affects spermatogenesis and discontinuation leads to recovery in most (5). In a 2006 meta-analysis of 1,549 eugonadal men treated with T, 94% recovered sperm counts of >20 million/mL after T cessation. The authors concluded that this incomplete recovery was likely due to variation in individual baseline sperm counts (5). However, recovery of spermatogenesis in men who are taking T and are infertile is unknown. The men who present with infertility and are presently taking T may not be the same population as the groups previously studied with normal semen parameters.

In the present study, we sought to study the use of T in men presenting for an infertility investigation. Specifically, we looked at patterns and frequency of T use in men presenting with infertility, and the semen and hormonal parameters of these men while on T and after cessation. This is the first study looking at T use in the infertile male population.

## MATERIALS AND METHODS

Men presenting for a fertility evaluation at a male infertility specialty clinic from 2008 to 2012 who reported taking T were identified via a prospectively collected database. Patients filled in a questionnaire that asked about medication use, including T. The data were subsequently validated by a clinician who asked specifically about medication use. These data were reviewed in a retrospective manner. For each medical record reviewed, we noted indication for therapy (symptom[s] or blood T), any pre- or post-T laboratory test results (serum hormones or semen testing), specialty of provider initiating T therapy, androgen preparation, dosage, dosing interval, and duration of therapy.

As a test of the accuracy of the patient reporting, we also used serum LH levels as a method to identify men who would have a high chance of being on T, but who had not reported being on T for the questionnaires. Serum LH <0.06 IU/L has been shown to be a reliable marker of exogenous T usage in healthy men in doping studies (6). A cutoff of LH <0.1 IU/L was used in the present study, because it was the lower limit of our assay. We subsequently made telephone contact with all of the men with LH levels <0.1 IU/L who had not reported to be on T and directly asked if they had ever used T as a means of testing the accuracy of our reporting.

The collection and analysis of the data were approved by the Research Ethics Board of the Mount Sinai Hospital.

Data were analyzed for semen and hormonal parameters while on T and after discontinuation. Blood samples for serum T were collected at several laboratories, based on patient convenience. Similarly, semen samples were collected at several laboratories, based on patient convenience. All andrology laboratories used validated methodologies and performed their own quality control procedures. Semen samples were collected at least 48 hours, but not more than 7 days, after the time of last ejaculation. After T discontinuation, when multiple semen analyses were obtained in follow-up, we chose the one obtained at least 3 months after T discontinuation. For men with multiple semen analyses after T discontinuation, we analyzed each semen analysis individually. For comparing semen parameters while on T and after being taken off, the Student *t* test was used, with $P < .05$ considered to be indicative of significant differences.

## RESULTS

During the study period, 4,400 men were seen in the male infertility clinic, and 59 (1.3%) were found to be on T at presentation. Fifty-six of these men reported taking T on their initial questionnaire and an additional 3 reported taking T when they were specifically asked about T use by the interviewing physician. Of the 4,400 men, hormone profiles were obtained for 3,650. Of these, 27 men were identified as having LH <0.1 IU/L. Of these, 9 had Kallman syndrome and the remaining 18 were contacted by phone to inquire about T usage. None of these men reported ever having taken T. Of the men identified to be on T, the mean age at presentation was 38.43 ± 8.62 years. The mean duration of treatment with T before presentation was 6.04 ± 7.08 years. Coexisting conditions included: Klinefelter syndrome (n = 8; 13.55%), history of bilateral undescended testicles (n = 7; 11.86%), Kallman syndrome (n = 5; 8.47%), Sertoli cell only syndrome (n = 2; 3.40%), chemotherapy-induced testicular failure (n = 2; 3.40%), prolactinoma (n = 2; 3.40%), opioid induced testicular failure (n = 2; 3.40%), and anejaculation (n = 1; 1.69%).

### Prescribing Patterns

Prescribers included: endocrinologists (n = 14; 23.73%), general practitioners (n = 10; 16.95%), urologists (n = 9; 15.25%), general gynecologists (n = 3; 5.08%), gynecologists specializing in reproductive endocrinology and infertility (REI; n = 2; 3.39%), primary care physician with a focus on fertility (n = 1; 1.69%), person from the gym (n = 1; 1.69%), internationally obtained (England, Pakistan, Egypt, Saudi Arabia; n = 5; 8.47%), independently obtained (n = 4; 6.80%), and not reported (n = 10; 16.95%).

Formulations and dosages included: intramuscular injection (n = 28; 47.46%), most commonly 200 mg every 2 weeks, range 50–300 mg every 2 weeks; transdermal gel (n = 26; 44.07%), most commonly 5 mg daily, range 5 mg every other day to 10 mg daily; oral Andriol (n = 3; 5.08%), 80 mg daily; pellet (n = 1; 1.69%), dose unknown; and unknown formulation and dose (n = 1; 1.69%). Other fertility-related medications reported being taken at the time of presentation included: hCG (n = 12), clomiphene citrate (n = 11), phosphodiesterase-5 inhibitors (n = 10), recombinant FSH (Puregon; n = 5), recombinant LH (Luveris; n = 1), anastrozole (n = 3), spironolactone (n = 2), DHEA (n = 1), and highly purified menotropin (Menopur; n = 1).

Reported indications for T replacement included: symptoms of hypogonadism and low serum T (n = 28; 47.46%), symptoms of hypogonadism (n = 16; 27.12%), infertility (n = 7; 11.86%), low serum T (n = 5; 8.47%), and athletic purposes (n = 3; 5.08%). Of men prescribed T for infertility, the prescribers and formulations were: REI (n = 2), gel; endocrinologist (n = 2), intramuscular injection; gynecologist (n = 1), gel; primary care physician with a focus on fertility (n = 1), gel; and general practitioner (n = 1), gel.

### Semen and Hormonal Testing

Of the 59 men presenting on T, 27 (45.7%) had semen and blood hormone testing only while on T, 26 (44.1%) had semen

analyses ± blood hormones on T and after discontinuation, and 6 (10.2%) had no blood or semen testing (Fig. 1). Of the 53 men with semen analyses while on T, the mean sperm concentration was 5.25 million/mL, with 39/53 being azoospermic. Of this group, there were nine who were also taking hCG or rFSH with a mean sperm concentration of 1.94 million/mL, with four being azoospermic. A group of four men were on clomiphene citrate, three of whom were azoospermic while on T, with a mean sperm concentration of 2.5 million/mL.

Sixteen men had serum hormone levels checked while on T and after cessation. While on T, the mean FSH was 2.60 ± 7.11 IU/L, LH 1.76 ± 4.38 IU/L, and T 24.59 ± 17.93 nmol/L. After T discontinuation, the mean FSH was 13.56 ± 14.45 IU/L ($P$=.0090), LH 7.33 ± 7.21 IU/L ($P$=.0113), and T 7.19 ± 5.45 nmol/L ($P$=.0011). The mean time between measurements was 8.52 months.

Twenty-six men had semen analyses on T and after discontinuation (Fig. 1; Table 1). The mean time between T cessation and the initial semen analysis measurement was 6.48 ± 5.33 months. Of these men, 12 were not on any other hormonal medications after T cessation. For all men having semen analyses on T and after discontinuation, the mean sperm count increased from 1.23 ± 5.28 million/mL to 32.15 ± 64.94 million/mL after T discontinuation ($P$=.023). A total of 23/26 men (88.4%) were azoospermic while on T. For this group, after T cessation the mean sperm concentration increased to 27.46 ± 67.40 million/mL. Not all men recovered spermatogenesis: 12/26 (46.2%) remained azoospermic despite repeated sperm testing for more than 6 months. The other sperm parameters, including ejaculate volume, sperm motility, and sperm morphology, did not change with T cessation.

Of the 26 men above, nine were taking other hormones concomitantly with T when initially assessed: four were on hCG alone, three were on clomiphene citrate alone, two were on highly purified menotropin (Repronex) alone, one was on anastrozole alone, two were on hCG and recombinant FSH (Puregon), one was on hCG and clomiphene citrate, and one was on hCG and highly purified menotropin (Repronex). Of these, seven remained azoospermic after discontinuation of T. Of these, three had underlying known conditions: Sertoli cell only syndrome (n = 1), Klinefelter syndrome (n = 1), and Kallman syndrome (n = 1). The remaining four persistently azoospermic men did not have a known underlying condition.

Within the group of men having semen analyses before and after T discontinuation, there were six with conditions potentially associated with azoospermia, including Klinefelter syndrome (n = 2), history of bilateral undescended testicles (n = 1), Sertoli cell only syndrome (n = 1), Kallman syndrome (n = 1), and chemotherapy-induced testicular failure from Hodgkin lymphoma (n = 1; Fig. 1; Table 2). When these men were excluded, the remaining cohort of 17 men without known causes for azoospermia was analyzed. Of these 17 men, 11 had a recovery of sperm in the ejaculate (64.7%). The remaining six men (35.5%) had no known previous cause for azoospermia and were persistently azoospermic after T cessation.

Men with oligospermia also improved after the cessation of T (Tables 1 and 2). There were two men with initial sperm concentrations ranging between >0 and 20 million/mL. For these men, the mean sperm concentration on T was 3.00 ± 2.82 million/mL, and after discontinuation it was 80.5 ± 13.44 million/mL ($P$=.093). There was one man with a sperm concentration of 27.2 million/mL while on T, which increased to 43.3 million/mL after discontinuation.

Of the 26 men for which we had semen testing while on T and after cessation, nine received no further hormonal treatment. For these men, five had improvement in their semen parameters and four remained persistently azoospermic or severely oligospermic. Six men were started on hCG, six on clomiphene citrate, three on anastrozole, and two on highly purified menotropin (Menopur).

After T discontinuation, when multiple semen analyses were obtained in follow-up, we chose the one obtained ≥3 months after T discontinuation. For the cohort of 26 men with semen analyses on T and after discontinuation, the mean time between T cessation and the initial semen analysis measurement was 6.48 ± 5.33 months. Four of the men, all initially azoospermic, had two semen analyses after T cessation. Two of these men remained persistently azoospermic: The initial semen analyses were performed at 4 and 5 months, and the second semen analyses were performed at 7 and 10 months, respectively. The third man recovered to a concentration of 0.9 million/mL at 3 months, and then 1 million/mL at 9 months. The fourth man recovered to 204 million/mL at 4 months, and then 207.5 at 9 months.

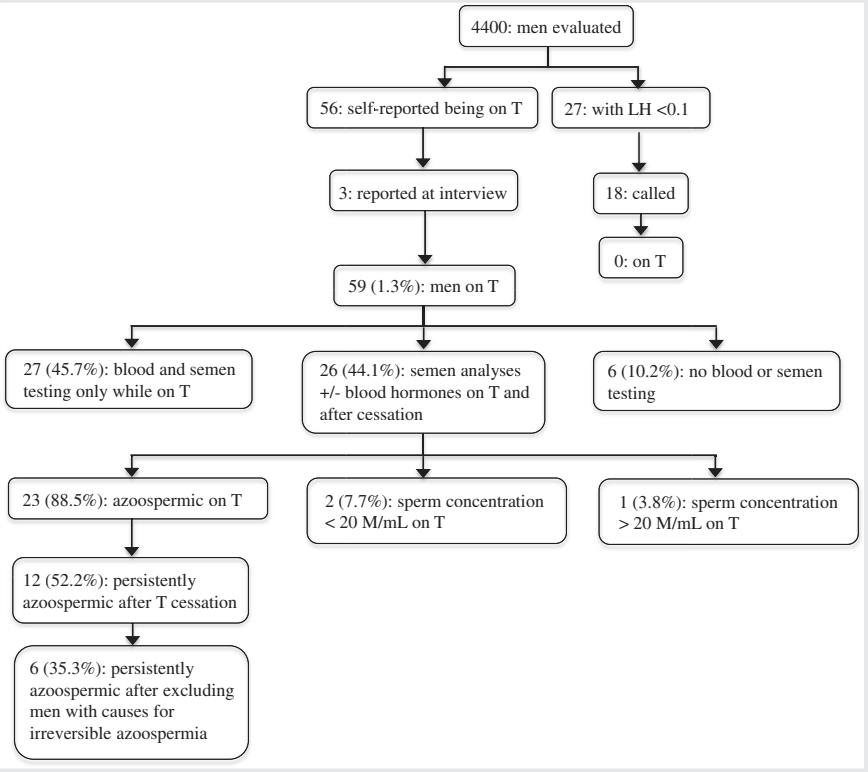
## DISCUSSION

Exogenous T suppresses both hypothalamic GnRH and pituitary FSH and LH production, resulting in a depletion of intratesticular T. The effect is a suppression of spermatogenesis so pronounced that it has been studied as a male hormonal contraceptive (7). In studies using T alone as a male contraceptive in fertile men, azoospermia was achieved in >90% of Asian men and ~60% of Caucasian men (8). It is clear that the spermatotoxic effects of T in fertile men are real.

Men presenting to infertility clinics represent a unique population of men who may be particularly susceptible to the spermatotoxic effects of exogenous T. In general, this population has some degree of baseline Leydig cell dysfunction, because low T or elevated LH has been shown to be present at baseline in 20%–30% of these men (9). Likewise, idiopathic infertile men have been shown to have 18% lower T, 26% lower calculated free T index, and 34% lower T/LH levels, compared with fertile control subjects (10). These intrinsic abnormalities may make the spermatotoxic effects of exogenous T even more pronounced compared with fertile counterparts.

Information on recovery of spermatogenesis after T cessation in infertile men is limited, but there are studies on the recovery in men with apparently normal fertility. In an integrated multivariate time-to-event analysis of data from 1,549 eugonadal men treated with T or T-progestagen male hormonal contraceptive regimens, Liu et al. (5) found that 94% of men recovered sperm counts of >20 million/mL by 1 year. Although the study was only of 1 year duration, it was projected that 100% of the men would recover

## FIGURE 1




Distribution of men presenting for a fertility evaluation from 2008 to 2012 on T.

*Samplaski. Testosterone use in infertile men. Fertil Steril 2013.*

spermatogenesis by 2 years. The projected timeline for recovery of spermatogenesis to counts >20 million/mL was 67% of men at 6 months and 100% at 24 months. Multivariate Cox analysis showed more rapid rates of recovery with, among other factors, shorter T treatment duration, shorter-acting T preparations, higher sperm concentrations at baseline, faster suppression of spermatogenesis, and lower blood concentrations of LH at baseline (5). Extrapolating these results to subfertile men, who at baseline have higher LH levels, would suggest that this population might have a longer duration of infertility following T cessation. Similarly, men using T as an anabolic-androgenic steroid have been shown to have recovery of spermatogenesis (11), although these men are presumed to be fertile at the start of T administration.

There are no published American Urological Association guidelines for T replacement therapy, and at this time the most commonly used guidelines are those of the Endocrine Society (1). According to those guidelines, men should be treated when they have consistent signs and symptoms and unequivocally low serum T levels. We found that only 47.46% of men referred to us were treated according to these guidelines. It is possible that some of the men that reported that they were treated for symptoms alone did have serum T checked at some point, but it is impossible to know this for certain. It is interesting that in the Endocrine Society guidelines, there is no caution of the spermatotoxic effects of T, and this may represent some of the physician lack of awareness of this effect.

## TABLE 1

**Sperm counts while on T and after discontinuation for all men with semen analyses while on T and after discontinuation.**

| | | Sperm count, million/mL (mean ± SD) | | |
|---|---|---|---|---|
| | **Azoospermic** | **Initial count < 20** | **Initial count > 20** | **All men** |
| No. of men | 23 | 2 | 1 | 26 |
| On T | 0 | 3.00 ± 2.82 | 27.20 | 1.23 ± 5.28 |
| After T discontinuation | 27.46 ± 67.40 | 80.50 ± 13.44 | 43.30 | 32.15 ± 64.94 |
| *P* value | .063 | .093 | | .023 * |

*Samplaski. Testosterone use in infertile men. Fertil Steril 2013.*

## TABLE 2

**Sperm counts while on T and after discontinuation for men with semen analyses while on T and after discontinuation, excluding men with causes for irreversible azoospermia.**[a]

| | Sperm count, million/mL (mean ± SD) | | | |
|---|---|---|---|---|
| | Azoospermic | Initial count < 20 | Initial count > 20 | All men |
| No. of men | 17 | 2 | 1 | 19 |
| On T | 0 | 3.00 ± 2.82 | 27.20 | 1.75 ± 6.27 |
| After T discontinuation | 36.89 ± 79.08 | 80.5 ± 13.44 | 43.30 | 41.82 ± 73.55 |
| *P* value | .082 | .093 | | .054 |

[a] Causes for irreversible azoospermia: Klinefelter syndrome (n = 2), history of bilateral undescended testicles (n = 1), Sertoli cell only syndrome (n = 1), Kallman syndrome (n = 1), history of Hodgkin lymphoma and chemotherapy (n = 1).

*Samplaski. Testosterone use in infertile men. Fertil Steril 2013.*

The most well known off-label use of T is as an androgenic steroid by professional athletes and bodybuilders to enhance muscle size and athletic performance (12). Some 30%–75% of professional athletes and bodybuilders in the United States have used steroids (13), and this group may use supraphysiologic doses, up to 100 times higher than physiologic replacement doses (13, 14). This population may be at high risk for the gonadotoxic effects of T replacement, which may be more dangerous at high doses and with prolonged use. Addressing spermatogenesis in this population, Kanayama et al. (15) suggest that many of these men are likely to experience clinically significant fertility-related side effects from anabolic-androgenic steroids (15, 16). Complicating this situation, men using T for athletic purposes are often fearful to disclose their use of illegal substances and subsequently do not report side effects (13, 17, 18). Pope et al. (17) studied a group of weightlifters, of whom 54% were anabolic-androgenic steroid users. Of those users, 56% had never revealed their androgen use to a physician (17) and 50% did not regard the knowledge of their physician regarding androgens as any more reliable than that of their friends, internet sites, or suppliers. In addition, many abusers concurrently take antiestrogens, aromatase inhibitors, and hCG to counteract the adverse effects of androgens and perhaps avert the detection of their use (15). Interestingly, very few of our patients admitted using T for athletic purposes. Certainly some of this may be an ascertainment bias, but very few of the men tested were found to have low LH levels (previously identified as an accurate marker for T doping for athletic purposes), which does suggest that in our population T use for athletic purposes was not common.

We found that the most common prescribers of T for infertile men were endocrinologists, followed by general practitioners and urologists. We were surprised to find that there are still practicing physicians prescribing T for the treatment of male infertility. This confirms the report by Ko et al. (19) finding that 25% of American urologists who answered their survey would consider T therapy as a reasonable option to manage men with infertility. Similarly, Ko et al.'s study found that patients using prescribed T were almost universally unaware of the potential negative impact of T on fertility.

The amount of T being prescribed continues to increase, as the indications for its use expand (20). In Canada, T was not commonly used by men presenting for fertility investigation (1.3%). However, in a recent American review of 1,540 men presenting for fertility evaluation, 7.1% of men were on T at the time of the initial assessment (21). Although this is an area with little published literature, it is likely that there is a significant difference in the utilization of T in different regions and countries.

Although all of the questionnaires were validated by the physician at the time of patient interview, our study was subject to reporting bias. Men may not disclose that they are taking T, particularly if their T use was illicit for athletic purposes. As a second validation, we studied all of the men with low LH values, which have previously been reported to be associated with illicit use of exogenous T for athletic purposes (6). These men were all called and they all denied using any T. The fact that there were very few men with low LH, and that these men denied using T, would indicate that T for athletic purposes was uncommon in our population.

We also do not really know how much information the men were given before being given prescriptions for T. We do not know if these men were counseled about the negative effects of T on fertility and if the prescribing physicians were aware of the gonadotoxic effects of exogenous T. As mentioned earlier, there is no caution of the spermatotoxic effects of T in the Endocrine Society guidelines, which may represent a source of physician miseducation.

Finally, 11/17 (64.7%) of the men with azoospermia with no other known potential causes recovered spermatogenesis when T was stopped. This is a lower recovery rate than in the studies on fertile subjects given T as a temporary contraceptive, but it must be remembered that only 67% of the men in the study on fertile men recovered spermatogenesis by 6 months, with 94% recovering by one year (5). Our study had an average 6 months of follow-up, so the rate of recovery of spermatogenesis in the infertile men is very similar to the rate of recovery reported at 6 months in the studies on fertile men. Potentially, some of these men would have recovered spermatogenesis if our study had been of longer duration. Alternatively, some of these men may have had some underlying spermatogenic defects which potentiated the gonadotoxic effects of T.

A subgroup of men on T who were less likely to have significantly improved semen parameters when the T was discontinued were those who were taking other hormones (hCG,

clomiphene citrate, rFSH, or aromatase inhibitors) concomitantly with the T. Of the nine men in this group who had semen testing before and after stopping the T, seven remained azoospermic. Excluding the three men with a known cause for azospermia, 4/6 (66%) of the men with no known underlying cause for azoospermia remained azoospermic when the T was discontinued. In contrast, for men on T not taking other hormones and with no known cause of azoospermia, only 2/11 (18%) remained azoospermic when the T was discontinued. The work by Lipshultz's group suggested that hCG could be used to prevent the adverse impact of exogenous T on spermatogenesis (22). This makes it likely that the group of men in our study who were azoospermic on T while taking concomitant hormones had an underlying unknown defect of spermatogenesis and explains why few of the men in this group had improved sperm parameters when the T was discontinued.

## Conclusion

In Canada, T was not commonly used by men presenting for fertility investigation. Infertile men on T represent a heterogeneous group with different underlying conditions, many of which could lead to infertility. Although 47.46% of men on T were treated in accordance with Endocrine Society guidelines, we were surprised to find that T was prescribed to treat infertility for 12% of the men.

T cessation resulted in a fairly rapid increase in sperm counts (1.23 million/mL to 32.15 million/mL). A subset of men with no other cause for the azoospermia remained azoospermic despite T cessation. This particular study had a an average follow-up period of 6 months; it is possible that with longer follow-up more of the men would have recovered spermatogenesis. Alternatively, some of these men may have had some underlying spermatogenic defects that potentiated the gonadotoxic effects of T. Although men in reproductive years should be discouraged from using T unless medically required, this study indicates that most infertile men who have no other cause for azoospermia recover spermatogenesis when T is discontinued.

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