Age and duration of testosterone therapy predict time to return of sperm count after human chorionic gonadotropin therapy

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Objective: To determine factors that influence sperm recovery after T-associated infertility.
Design: Clinical retrospective study.
Setting: Academic male-infertility urology clinic.
Patient(s): Sixty-six men who presented with infertility after T use.
Intervention(s): T cessation and combination high-dose hCG and selective estrogen modulator (SERM) therapy.
Main Outcome Measure(s): Whether patients successfully achieved or failed to achieve a total motile count (TMC) of greater than 5 million sperm within 12 months of T cessation and initiation of therapy.
Result(s): A TMC of greater than 5 million sperm was achieved by 46 men (70%). Both increased age and duration of T use directly correlated with time to sperm recovery at both 6 and 12 months of hCG/SERM therapy. Age more consistently limited sperm recovery, while duration of T use had less influence at 12 months than at 6 months. Only 64.8% of azoospermic men achieved a TMC greater than 5 million sperm at 12 months, compared with 91.7% of cryptozoospermic men, yet this did not predict a failure of sperm recovery.
Conclusion(s): Increasing age and duration of T use significantly reduce the likelihood of recovery of sperm in the ejaculate, based on a criterion of a TMC of 5 million sperm, at 6 and 12 months. Physicians should be cautious in pursuing long-term T therapy, particularly in men who still desire fertility. Using these findings, physicians can counsel men regarding the likelihood of recovery of sperm at 6 and 12 months. (Fertil Steril® 2017;107:351–7. ©2016 by American Society for Reproductive Medicine.)
Key Words: Infertility, testosterone, sperm, azoospermia, human chorionic gonadotropin, spermatogenesis-blocking agents

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The use of exogenous T in the treatment of hypogonadism has known risks with regards to male factor infertility. Serum T levels in men begin to decrease in an age-dependent manner starting in the late 30s (1–3), and the number of T prescriptions has drastically increased in recent years, from 1.2 million patients in 2010 to 2.2 million patients in 2013 (4). Of men receiving T therapy (TTh), 12.4% were younger than 39 years old, indicating that a large number of men seek TTh during the reproductive years (5). One study found that 7% of male patients seeking care for infertility were on TTh at the time of their visit, and concomitant TTh was the fourth most common etiology of male factor infertility in the two large infertility practices in the study (6). Coupled with the increase in T prescriptions, physicians are often failing to inform patients of the risk of T-induced infertility, in part due to a lack of knowledge of the fertility-related adverse effects of TTh. In a 2010 survey of urologist members of the American Urological Association, 25% incorrectly believed that TTh would improve a man's fertility (7); such beliefs likely contribute to the growing number of men with T-induced infertility (8).

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Exogenous T inhibits spermatogenesis by suppressing secretion of FSH and LH from the anterior pituitary gland, limiting the signals required for endogenous T production and spermatogenesis (9). Thus, the use of T by younger men increasingly intersects with their reproductive potential for many men, and approaches to predicting and mitigating the negative effects of T on fertility are needed.

Several studies have demonstrated that cessation of TTh in men seeking fertility treatment can lead to a return to baseline sperm concentrations (6, 10–12). However, the time for return of sperm to the ejaculate in quantities sufficient for fertility remains unclear. In a pooled analysis of 30 studies using T as a short-term hormonal contraceptive in eugonadal men, Liu et al. demonstrated that the average probability of sperm recovery to 20 million sperm/mL was 67% within 6 months, 90% within 12 months, 96% within 16 months, and 100% within 24 months but suggested that men who started with a low-normal sperm count and who were older required more time to recover (10). Another study examining more than 14,000 semen samples from World Health Organization studies in which androgens were evaluated as a potential male contraceptive found that sperm production after therapy was only approximately 85% of pretreatment concentrations (11). The literature also suggests that men who have been on high-dose TTh for longer periods will require longer to recover normal sperm production (12, 13).

HCG and selective estrogen receptor modulators (SERMs) are effective at restoring spermatogenesis alone and in combination (12, 14–17). The efficacy of hCG is attributed to its structural similarity to LH. SERMs potentiate spermatogenesis by inhibiting negative feedback by estrogen, thereby raising GnRH and gonadotropin levels and increasing downstream T production. Numerous protocols combining hCG and SERMs are available for the restoration of endogenous T in T-suppressed men. Ishikawa et al. used 5,000 IU of hCG 3 times a week for 3–6 months, in combination with recombinant FSH supplementation, with recovery of spermatogenesis observed in 44%–100% of patients (18). HCG doses described in the literature range from 3,000 to 10,000 IU, administered 2–3 times per week (8, 13, 15, 18, 19). In a retrospective chart review of azoospermic or severely oligospermic men, Wenker et al. observed return of spermatogenesis in a mean of 4.6 months with a mean density of 22 million sperm/mL in 95.9% of subjects receiving hCG 3,000 IU every other day, along with either FSH, clomiphene citrate, tamoxifen, or anastrozole (12). In another retrospective review by Coward et al., men previously on TTh and seeking vasectomy reversal were treated with high-dose hCG (3,000 IU every other day) and clomiphene citrate, with 83% having normalization of LH, FSH, and T levels (15).

Previous studies analyzed only patients who had been on T for a short duration, for contraception purposes, or who were eugonadal at the time of TTh initiation; our study analyzes men with a prolonged duration of TTh use and focuses on men who were cryptozoospermic or azoospermic at cessation of TTh. The primary objective of the present study is to determine the factors that influence sperm recovery after presumed T-associated infertility.

MATERIALS AND METHODS

Patient Selection

After Institutional Review Board approval, we retrospectively reviewed the records of 66 men with T-associated infertility who were evaluated at a single academic infertility clinic between 2004 and 2015. Men were included if they presented for infertility, were 18 years or older, had been on T for a recorded duration, and were found to be azoospermic or cryptozoospermic (<1 million sperm/mL) at the time of TTh cessation. In addition, they must have ceased TTh and begun hCG therapy within a single visit and had a least one follow-up semen analysis. Men were excluded if they had a history of vasectomy, obstructive azoospermia, or a known primary cause of testicular failure such as chromosomal abnormalities, Y-chromosome microdeletions, history of testicular trauma or infection, or history of cryptorchidism. No men included in the analysis were concurrently on recombinant FSH. Age at time of T cessation, total duration of TTh use, route of TTh, duration and dosage of hCG therapy, use and type of SERM, serum levels of T, FSH, and LH at time of presentation, and sperm concentration at presentation were recorded and compared.

Treatment

At initial presentation, men underwent a physical examination by a urologist with fellowship training in male reproductive medicine, as well as evaluation of serum T, LH, FSH, PRL, and E_2 levels and semen analysis. Men were instructed to stop T use and begin a regimen of 3,000 IU of hCG administered SC 3 times per week. All men in this study were also prescribed either clomiphene citrate or tamoxifen citrate. Patients were seen in follow-up approximately every 3 months, with semen analyses and hormonal evaluation performed at each visit.

Statistical Analysis

The main outcome measure was whether patients achieved a total motile sperm count (TMC) of greater than 5 million sperm during evaluation within 6 months or within 12 months of stopping TTh and beginning hCG therapy. This TMC reflects the minimum number of sperm used for IUI at our institution. Two binary variables (TMC >5 million reached within 12 months or within 6 months) were created, which were the dependent variables of interest.

We compared the patient characteristics between those who reached TMC >5 million within 12 months using the Student's *t*-test for normally distributed continuous variables, the Mann-Whitney *U*-test for nonparametric continuous variables, and the χ^2-test or Fisher's exact test for categorical variables. Only duration of TTh was found to be a nonparametric variable.

We used a multivariate linear probability model to estimate the effects of various factors on successfully reaching a TMC of >5 million sperm. Six independent variables were used in the final model—three continuous variables (duration of TTh, age at TTh cessation, and T level at presentation) and three categorical variables (whether TTh was delivered by IM injection, transdermal application, or pellet insertion; use of

clomiphene or tamoxifen citrate; and presence of cryptozoospermia or azoospermia). We then used the results of this regression analysis to calculate the predicted probability of achieving a TMC >5 million within 12 months and 6 months at different ages and durations of TTh. For example, to calculate the predicted probability of success for a 30-year-old man with a TTh duration of 1 year, we assumed every patient in our sample is 30 years old and was on TTh for 1 year. We then used the coefficients estimated from the regression to calculate each patient's predicted probability of success. These probabilities were then averaged across the entire sample to calculate the final predicted probability for those parameters. We repeated this process for each combination of age and duration of TTh. All statistical analysis was performed using STATA 14.1, with $P<.05$ considered statistically significant.

RESULTS

Sixty-six men met the criteria and were included in this analysis at 12 months. Table 1 shows the baseline characteristics of all men and is further stratified by those who successfully achieved a TMC >5 million sperm within 12 months and those who did not. The mean ± SD age of the cohort was 40.2 ± 8.7 years, and the median duration of TTh was 2 years (range 0.17–25) years. Thirty-five men used IM injections of T, 22 used topical T, and nine used pellets. Forty-six men (69.7%) successfully achieved a TMC of 5 million or greater within 12 months. For men with successful recovery of spermatogenesis, the mean ± SD age was 38.3 ± 7.0 years and duration of TTh use was a median of 1.67 (range 0.17–15) years. For men without successful recovery of spermatogenesis, the mean ± SD age was 44.0 ± 10.7 years and median duration of TTh was 4.0 (range 0.25–25) years. The average TMC for men with a TMC >5 million sperm within 12 months was 40.0 ± 44.6 million sperm, while the average for those men with a TMC <5 million sperm was 1.8 ± 1.6 million sperm. The average sperm density for men who achieved a TMC >5 million sperm within 12 months was 33.9 ± 36.8 million sperm/mL, while the average sperm density for those with a TMC <5 million sperm was 4.7 ± .1 million sperm/mL. Table 2 denotes semen parameters, FSH, LH, and T levels for each formulation of T at baseline, at 6 months, and at 12 months. Semen density and TMC increase at each evaluation, from baseline to 6 months to 12 months, demonstrating the waning effect of T over time.

When comparing the differences between men who did and did not have successful recovery of spermatogenesis, age ($P=.018$) and duration of TTh ($P=.006$) were identified as significant predisposing factors. Route of T administration, initial serum T level, type of SERM used, and initial sperm concentration were not found to be significant predictors of sperm recovery. Multivariate linear regressions were performed to determine the magnitude of effect on the likelihood of success at both 6 and 12 months; correlation coefficients are reported in Table 3. Supplemental Table 1 compares the result of a multivariate linear regression including limited predictors with a multivariate linear regression with an expanded number of predictors, demonstrating that the expanded model accounts for a larger proportion of the variance in sperm recovery. Results presented here use the results of the expanded regression.

Duration of TTh, age at TTh cessation, and initial sperm concentration were significant predictors for successfully reaching a TMC of 5 million within 12 months. Duration of TTh has a correlation coefficient of −0.0306 ($\rho = 0.017$; 95% confidence interval [CI], −0.0555, −0.0057), suggesting that the probability of reaching a TMC of 5 million sperm decreases by 3.06% for each additional year of TTh. Age has a correlation coefficient of −0.0171 ($\rho = 0.015$; 95% CI, −0.0308, −0.0034), which suggests that the probability of reaching a TMC of 5 million decreases by 1.71% for every year of age.

The regression analysis was performed for sperm recovery at 6 months using 59 observations. Similar to the analysis of

TABLE 1

Baseline characteristics and comparison of men with successful and unsuccessful sperm recovery.

Biometric feature	All men (n = 66)	Success (n = 46)	Failure (n = 20)	*P* value
Age of men (y)	40.2 (±8.7)	38.3 (±7.0)	44.8 (±10.5)	.018
Time on TTh (y)	2.0 (0.17–25)	1.67 (0.17–15)	4.0 (0.25–25)	.001
Initial hormone analysis				
T (ng/dL)	632 (±369)	656 (±387)	577 (±327)	.654
FSH (mIU/mL)[a]	1.3 (±3.0)	1.2 (±3.1)	1.6 (±2.5)	.372
LH (mIU/mL)[a]	0.9 (±2.5)	0.9 (±2.8)	0.9 (±1.6)	.725
Route of T				
Injection	35 (53.0)	23 (50.0)	12 (60.0)	.654
Topical	22 (33.3)	17 (37.0)	5 (25.0)	
Pellets	9 (13.6)	6 (13.0)	3 (15.0)	
SERM				
Clomiphene citrate	45 (68.2)	32 (69.6)	13 (65.0)	.859
Tamoxifen citrate	21 (31.8)	14 (30.4)	7 (35.0)	
Fertility diagnosis				
Azoospermia	54 (81.8)	34 (76.1)	19 (95.0)	.055
Cryptozoospermia	12 (18.2)	11 (23.9)	1 (5.0)	

Note: Data are presented as mean (±SD), median (range), or n (%).
[a] Missing information in some subjects.

Kohn. Sperm recovery after T use. Fertil Steril 2016.

TABLE 2

Median hormone levels and semen parameters for patients receiving testosterone via intramuscular injection, transdermal, and pellets at baseline, 6 months, and 12 months.

		Initial evaluation							Evaluation within 6 mo		
T Type	Subgroup	FSH	LH	T	Semen volume	Semen density	Semen mobility	TMC	FSH	LH	T
Injection (n = 35)	All patients	0.4 (0.1–2.0)	0.2 (0.02–0.5)	630 (395–1,030)	2.5 (1.5–3.5)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	1.35 (0.8–4.0)	2.4 (0.3–4.8)	536 (245–585)
	<5 TMC (n = 13)	0.70 (0.1–2.0)	0.3 (0.08–0.6)	509 (431–638)	2.8 (1.5–3.3)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	2.0 (0.2–3.5)	0.6 (0.07–3.3)	585 (561–612)
	>5 TMC (n = 22)	0.4 (0.1–0.7)	0.1 (0.01–0.4)	772 (316–1,059)	2.25 (1.5–3.5)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	1.0 (0.9–5.0)	2.8 (1.6–5.3)	386 (233–561)
Topical (n = 22)	All patients	0.3 (0.07–0.6)	0.1 (0.04–0.4)	532 (371–774)	2.4 (1.5–3.0)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	1.4 (0.7–2.6)	0.9 (0.3–1.9)	418 (291–564)
	<5 TMC (n = 6)	0.4 (0.0–0.7)	0.07 (0.03–0.3)	657 (512–816)	3.25 (1.9–3.9)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	1.3 (1.0–3.7)	1.3 (0.7–1.7)	499 (370–535)
	>5 TMC (n = 16)	0.4 (0.09–0.7)	0.1 (0.1–0.6)	527 (312–721)	2.0 (1.5–3.0)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	1.5 (0.7–2.5)	0.8 (0.3–2.5)	402 (300–567)
Pellet (n = 9)	All patients	0.7 (0.3–3.2)	0.3 (0.2–1.4)	559 (208–703)	1.8 (1.1–2.0)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	2.0 (0.2–5.6)	0.2 (0.1–2.6)	566 (278–777)
	<5 TMC (n = 3)	0.8 (0.5–5.4)	0.4 (0.3–2.2)	460 (334–587)	1.0 (0.6–1.5)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	2.0 (0.7–3.6)	0.7 (0.2–3.8)	422 (216–716)
	>5 TMC (n = 6)	0.7 (0.5–4.0)	0.4 (0.2–1.6)	459 (207–673)	1.5 (1.0–2.0)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)	2.9 (0.2–6.9)	0.2 (0.1–2.1)	707 (492–777)

Note: Data are presented as median (interquartile range).

Kohn. Sperm recovery after T use. Fertil Steril 2016.

the 12-month data, duration of TTh ($\rho = -0.0555$, $P<.001$; 95% CI, −0.0771, −0.0339) and age ($\rho = -0.0163$, $P=.019$; 95% CI, −0.0298, −0.0028) were identified as significant negative predictors of successful sperm recovery at 6 months. Using the probabilities generated from this linear probability model, the likelihood of sperm recovery at 12 and 6 months based on a man's age and duration of TTh was calculated (Figs. 1A and 1B).

DISCUSSION

Currently, no guidelines are available discussing the management of men presenting with infertility that is presumed to be associated with T use. Furthermore, it is unclear how soon after cessation of T that adequate spermatogenesis should be anticipated. The results of this study facilitate physician counseling of men presenting with azoospermia or cryptozoospermia presumably due to TTh and provide a means to estimate the likelihood of recovered spermatogenesis at 6 and 12 months after discontinuing TTh. The coefficients for the impact of age are similar at both 6 and 12 months (−0.016 and −0.017), indicating that age has a durable, long-lasting effect on sperm production and recovery of spermatogenesis. In contrast, the contribution of the duration of TTh decreased by approximately 50% between the 6 and 12 month analyses (−0.055 vs. −0.030), suggesting that the deleterious impact of TTh on spermatogenesis diminishes with increasing time off of T.

TTh suppresses the hypothalamic-pituitary-gonadal axis and inhibits spermatogenesis within 3.5 months in most men (10, 20–22). The present study examined the successful return of spermatogenesis after discontinuation of TTh and initiation of high-dose hCG and SERM therapy. We found that cryptozoospermic men had a higher likelihood of successful recovery of spermatogenesis when compared with azoospermic men at 12 months but not at 6 months. Of azoospermic men, only 64.8% achieved a TMC >5 million sperm at 12 months, compared with 91.7% of cryptozoospermic men. Thus, sperm recovery progresses at similar rates in both groups during the first 6 months, but cryptozoospermic men have a higher likelihood of successful recovery of spermatogenesis within 12 months.

In a preliminary study, we demonstrated that hCG therapy promotes sperm recovery after presumed T-associated infertility (12). In the present study, important new findings are observed. Our preliminary work defined recovery of spermatogenesis in azoospermic patients as the presence of *any* sperm and as *any* increase in sperm count for oligospermic patients. Our current study sets a more clinically relevant benchmark for sperm recovery—the desirable number of total motile sperm required for IUI. Furthermore, our preliminary work did not evaluate the effects of total duration of TTh, which are more clearly outlined. In the present study, our inclusion criteria are stricter and draw from a larger cohort of men, facilitating a more rigorous set of conclusions, and we concurrently assess factors that influence sperm recovery.

Most studies that have examined time to recovery of spermatogenesis after TTh have used T as a male contraceptive in eugonadal men for up to 18 months (20–24). In a pooled analysis of 30 hormone contraception studies encompassing 2,023 men, Liu et al. found age, initial T level, initial LH level, total duration of T, initial semen volume and density, and type of T to be significant predictors for recovery of spermatogenesis (10). However, this study examined men who were in tightly controlled

TABLE 2

Continued.

Evaluation within 6 mo							Evaluation within 12 mo			
Semen volume	Semen density	Semen mobility	TMC	FSH	LH	T	Semen volume	Semen density	Smen mobility	TMC
2.5 (1.5–3.5)	10.0 (5.3–20.0)	50 (33–65)	11.4 (3.9–25.6)	3.0 (1.0–5.0)	2.0 (0.3–4.0)	490 (275–662)	2.5 (1.5–3.0)	11.6 (5.1–24.9)	45 (30–64)	15.8 (3.9–36.5)
1.8 (1.4–2.6)	4.6 (1.8–6.4)	28 (25–40)	2.2 (1.3–3.6)	2.0 (0.2–3.5)	0.5 (0.06–3.3)	578 (612–473)	1.5 (1.0–2.4)	3.6 (1.3–5.1)	30 (25–40)	2.1 (0.9–3.3)
2.5 (2.0–3.6)	16.0 (21.7–9.1)	60 (48–65)	21.2 (10.9–36.4)	3.0 (1.0–6.2)	2.5 (1.2–3.8)	394 (257–639)	3.0 (2.0–3.5)	20.4 (9.2–32.1)	58 (44–65)	29.8 (46.9–14.9)
2.0 (1.1–2.4)	17.2 (7.2–41.2)	53 (43–60)	9.7 (4.4–21.4)	2.8 (0.9–4.8)	1.7 (0.3–3.0)	386 (265–551)	2.0 (2.0–2.7)	18.0 (6.7–47.6).	50 (42–60)	18.0 (5.6–61.8)
3.3 (2.0–4.0)	1.6 (0.5–4.6)	44 (15–55)	1.95 (0.3–3.7)	5.5 (4.1–9.8)	2.5 (1.8–5.0)	370 (221–499)	2.7 (2.0–3.8)	1.3 (0.6–2.4)	40 (16–52)	1.2 (0.1–3.2)
2.0 (1.0–2.0)	20.4 (16.3–47.6)	55 (45–60)	18.0 (8.8–27.7)	2.0 (0.7–3.0)	0.7 (0.3–3.0)	386 (282–588)	2.0 (2.0–2.1)	20.5 (16.3–57.2)	53 (46–60)	22.9 (9.2–71.7)
1.5 (0.9–2.0)	14.5 (2.2–23.5)	45 (31–52)	4.48 (0.9–16.1)	2.0 (0.2–5.6)	0.24 (0.2–3.7)	542 (367–707)	2.0 (1.0–2.5)	24.0 (32.7–12.8)	40 (34–55)	9.6 (1.3–45.0)
2.0 (1.0–2.0)	1.5 (0.8–4.5)	30 (25–50)	0.75 (0.4–1.2)	2.0 (1.1–10)	0.24 (0.2–6.1)	566 (422–866)	1.0 (0.7–2.0)	4.5 (2.6–8.3)	30 (15–40)	1.2 (0.6–1.3)
1.0 (0.8–2.0)	24.0 (21.9–27.2)	53.0 (40–54)	18.3 (9.6–23.5)	2.6 (0.4–5.3)	1.8 (0.2–3.5)	500 (390–666)	2.0 (1.3–2.4)	30.0 (24.8–52.1)	48 (36–67)	39.4 (15.7–78.4)

Kohn. Sperm recovery after T use. Fertil Steril 2016.

clinical trials, were eugonadal before TTh, and were only on T for less than 1 year on average, limiting the generalizability of the results to hypogonadal men on longer-duration TTh (8). Nevertheless, the probabilities of recovery of spermatogenesis in the present study are comparable to those observed by Liu et al. (10). Liu et al. calculate a 90% chance of recovery to 20 million sperm/mL 12 months after cessation of T with a mean cohort age of 31.8 years and duration of T treatment of 9.45 months. This probability is similar to our calculated probability of a 90.0% chance of achieving a TMC >5 million sperm at 12 months for a 30-year-old man with a 1-year duration of TTh, yet Liu et al. find a lower average sperm density than our 33.9 million sperm/mL average. When comparing probabilities of sperm recovery at 6 months duration of TTh, those calculated by Liu et al. are lower than those calculated by our model. Our increased probabilities may be attributable to accelerated sperm recovery from hCG and SERM therapy.

While the only significant predictors in our univariate analysis were time on T and age, we included initial T levels, route of T administration, and initial oligospermia because Liu et al. demonstrated in a much larger population that these factors are significant; additionally, the inclusion of these variables strengthened the fit of our model. Yet our model differs from that of Liu et al. in that our model calculates probabilities for recovery of spermatogenesis for a wider range of ages and longer duration of T in a population of men for whom these data will provide a meaningful basis for patient counseling.

A factor in the growing prevalence of T-associated infertility is the mistaken view that T can improve a man's fertility (7). As such, it is essential that physicians counsel patients that T will reduce their fertility and that longer durations of

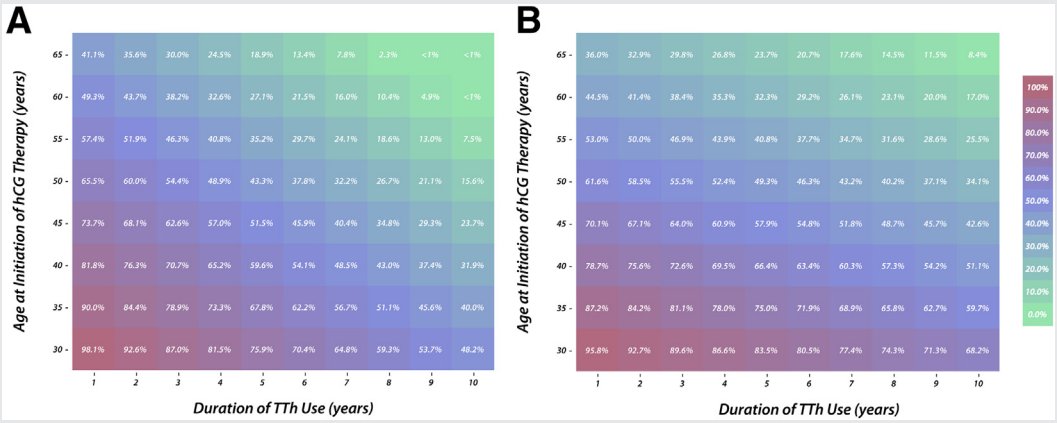
TABLE 3

Multivariate linear regression.

	6-mo analysis			12-mo analysis		
Variable	Coefficient (SE)	95% CI	*P* value	Coefficient (SE)	95% CI	*P* value
Time on TTh (y)	−0.0555	(−0.0771, −0.0339)	<.001	−0.0306	(−0.0555, −0.0057)	.017
Age (y)	−0.0163	(−0.0298, −0.0028)	.019	−0.0171	(−0.0308, −0.0034)	.015
Initial T (ng/dL)	0.0002	(−0.0001, 0.0005)	.176	0.00002	(−0.0002, 0.0002)	.866
Clomiphene citrate	−0.0641	(−0.3045, 0.1763)	.595	0.0094	(−0.2179, 0.2366)	.935
Cryptospermic (million sperm/mL)	0.184	(0.0700, 0.4390)	.152	0.2180	(−0.006, 0.4410)	.056
Type of T (reference: injection)						
Transdermal	0.0451	(−0.2154, 0.3055)	.730	0.124	(−0.1380, −0.3870)	.347
Pellet	0.177	(−0.076, 0.430)	.166	0.163	(−0.1100, 0.4360)	.237

Kohn. Sperm recovery after T use. Fertil Steril 2016.

FIGURE 1



(**A**) Probability of achieving a TMC greater than 5 million sperm within 12 months of TTh cessation. (**B**) Probability of achieving a TMC greater than 5 million sperm within 6 months of TTh cessation.

Kohn. Sperm recovery after T use. Fertil Steril 2016.

T or advanced age will prolong time to recovery of spermatogenesis. For men who desire future fertility, physicians should consider a baseline semen analysis before initiating TTh. This will ensure that men with underlying testicular dysfunction are identified before TTh, which could otherwise confound the interpretation of semen analyses while on post-TTh treatment.

The present study has several strengths and limitations. This is the first study to examine sperm recovery after long-term TTh. We observed that both age and duration of TTh are predictors of recovery of spermatogenesis and present a model that facilitates risk stratification across a broad range of ages and TTh durations. Nevertheless, the retrospective nature of the study limits the impact and generalizability of the data. Importantly, we do not have semen analyses or FSH levels for these men before starting TTh, limiting our ability to discern underlying testicular dysfunction before initiation of TTh. While we excluded men with known genetic or other known causes of infertility, we cannot conclude that all men included in this analysis were azoospermic or cryptospermic solely due to T-induced infertility. Our model, however, is still clinically useful as many patients who present with infertility that is presumed to be associated with T use do not have a semen analysis before initiating T use. Additionally, our strict inclusion criteria limited the number of men included in this analysis. Finally, the dependent variable in our analysis is whether men successfully achieved a TMC >5 million sperm within 6 or 12 months; however, we did not observe each subject's TMC at exactly 6 or 12 months after initiation of hCG/SERM therapy, but rather the semen analysis occurred within or up to 6 and 12 months after therapy initiation. Therefore, it is likely that we underestimate the effects of the predictor variables on TMC recovery.

Conclusions

The increased use of TTh in younger men has led to a rise in T-associated infertility. In our retrospective study of 66 men with T-associated infertility who ceased TTh and began high-dose hCG and/or SERM therapy, we identified age and duration of TTh as significant predictors for the recovery of spermatogenesis at 6 and 12 months after TTh cessation. Using our predictive model, physicians can counsel men regarding the likelihood of recovery of spermatogenesis at 6 and 12 months after TTh cessation. Older men on long-term TTh in particular should be counseled regarding the lower probability of successful recovery of spermatogenesis.

REFERENCES

1. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:2536–59.
2. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724–31.
3. McKinlay JB, Link CL. Measuring the urologic iceberg: design and implementation of the Boston Area Community Health (BACH) Survey. Eur Urol 2007;52:389–96.
4. Nguyen CP, Hirsch MS, Moeny D, Kaul S, Mohamoud M, Joffe HV. Testosterone and "age-related hypogonadism"—FDA concerns. N Eng J Med 2015;373:689–91.
5. Layton JB, Li D, Meier CR, Sharpless JL, Sturmer T, Jick SS, et al. Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. J Clin Endocrinol Metab 2014;99:835–42.
6. Kolettis PN, Purcell ML, Parker W, Poston T, Nangia AK. Medical testosterone: an iatrogenic cause of male infertility and a growing problem. Urology 2015;85:1068–72.
7. Ko EY, Siddiqi K, Brannigan RE, Sabanegh ES Jr. Empirical medical therapy for idiopathic male infertility: a survey of the American Urological Association. J Urol 2012;187:973–8.
8. McBride JA, Coward RM. Recovery of spermatogenesis following testosterone replacement therapy or anabolic-androgenic steroid use. Asian J Androl 2016;18:373–80.
9. MacIndoe JH, Perry PJ, Yates WR, Holman TL, Ellingrod VL, Scott SD. Testosterone suppression of the HPT axis. J Invest Med 1997;45:441–7.

10. Liu PY, Swerdloff RS, Christenson PD, Handelsman DJ, Wang C. Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. Lancet 2006;367:1412–20.
11. Ly LP, Liu PY, Handelsman DJ. Rates of suppression and recovery of human sperm output in testosterone-based hormonal contraceptive regimens. Hum Reprod 2005;20:1733–40.
12. Wenker EP, Dupree JM, Langille GM, Kovac J, Ramasamy R, Lamb D, et al. The use of hCG-based combination therapy for recovery of spermatogenesis after testosterone use. J Sex Med 2015;12:1334–7.
13. Menon DK. Successful treatment of anabolic steroid-induced azoospermia with human chorionic gonadotropin and human menopausal gonadotropin. Fertil Steril 2003;79(Suppl 3):1659–61.
14. Liu PY, Turner L, Rushford D, McDonald J, Baker HW, Conway AJ, et al. Efficacy and safety of recombinant human follicle stimulating hormone (Gonal-F) with urinary human chorionic gonadotrophin for induction of spermatogenesis and fertility in gonadotrophin-deficient men. Hum Reprod 1999;14:1540–5.
15. Coward RM, Mata DA, Smith RP, Kovac JR, Lipshultz LI. Vasectomy reversal outcomes in men previously on testosterone supplementation therapy. Urology 2014;84:1335–40.
16. Rahnema CD, Lipshultz LI, Crosnoe LE, Kovac JR, Kim ED. Anabolic steroid-induced hypogonadism: diagnosis and treatment. Fertil Steril 2014;101:1271–9.
17. Coviello AD, Matsumoto AM, Bremner WJ, Herbst KL, Amory JK, Anawalt BD, et al. Low-dose human chorionic gonadotropin maintains intratesticular testosterone in normal men with testosterone-induced gonadotropin suppression. J Clin Endocrinol Metab 2005;90:2595–602.
18. Ishikawa T, Ooba T, Kondo Y, Yamaguchi K, Fujisawa M. Assessment of gonadotropin therapy in male hypogonadotropic hypogonadism. Fertil Steril 2007;88:1697–9.
19. Gill GV. Anabolic steroid induced hypogonadism treated with human chorionic gonadotropin. Postgrad Med J 1998;74:45–6.
20. Hay CJ, Brady BM, Zitzmann M, Osmanagaoglu K, Pollanen P, Apter D, et al. A multicenter phase IIb study of a novel combination of intramuscular androgen (testosterone decanoate) and oral progestogen (etonogestrel) for male hormonal contraception. J Clin Endocrinol Metab 2005;90:2042–9.
21. Kinniburgh D, Zhu H, Cheng L, Kicman AT, Baird DT, Anderson RA. Oral desogestrel with testosterone pellets induces consistent suppression of spermatogenesis to azoospermia in both Caucasian and Chinese men. Hum Reprod 2002;17:1490–501.
22. Amory JK, Anawalt BD, Bremner WJ, Matsumoto AM. Daily testosterone and gonadotropin levels are similar in azoospermic and nonazoospermic normal men administered weekly testosterone: implications for male contraceptive development. J Androl 2001;22:1053–60.
23. Turner L, Conway AJ, Jimenez M, Liu PY, Forbes E, McLachlan RI, et al. Contraceptive efficacy of a depot progestin and androgen combination in men. J Clin Endocrinol Metab 2003;88:4659–67.
24. World Health Organization Task Force on Methods for the Regulations of Male Fertility. Rates of testosterone-induced suppression to severe oligozoospermia or azoospermia in two multinational clinical studies. Int J Androl 1995;18:157–65.

SUPPLEMENTAL TABLE 1

Additional multivariate linear regressions with different combinations of variables.

	6-mo analysis		12-mo analysis	
	Three variables	**Six variables**	**Three variables**	**Six variables**
Time on T (y)	−0.0568[c] (0.0110)	−0.0555[c] (0.0108)	−0.0330[c] (0.0115)	−0.0306[b] (0.0124)
Age (y)	−0.0128[b] (0.00593)	−0.0163[b] (0.00674)	−0.0154[c] (0.00576)	−0.0171[b] (0.00684)
Cryptospermic (million sperm/mL)	0.167 (0.129)	0.184 (0.127)	0.190[a] (0.109)	0.218[a] (0.112)
Initial T (ng/dL)		0.000196 (0.000143)		0.0000223 (0.000132)
Clomiphene citrate		−0.0641 (0.120)		0.00936 (0.114)
T type (reference: injection)				
Transdermal		0.0451 (0.130)		0.124 (0.131)
Pellet		0.177 (0.126)		0.163 (0.136)
Constant	1.361[c] (0.233)	1.369[c] (0.308)	1.407[c] (0.217)	1.377[c] (0.288)
N	59	59	66	66
R^2	0.302	0.340	0.277	0.297

Note: Robust standard errors are in parentheses.
[a] $P < .1$.
[b] $P < .05$.
[c] $P < .01$.

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