ORIGINAL ARTICLE: ANDROLOGY

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® 2016;■:■–■. ©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