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® 2014;101:64–9. ©2014 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