Concomitant Intramuscular Human Chorionic Gonadotropin Preserves Spermatogenesis in Men Undergoing Testosterone Replacement Therapy

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Purpose: Testosterone replacement therapy results in decreased serum gonadotropins and intratesticular testosterone, and impairs spermatogenesis, leading to azoospermia in 40% of patients. However, intratesticular testosterone can be maintained during testosterone replacement therapy with co-administration of low dose human chorionic gonadotropin, which may support continued spermatogenesis in patients on testosterone replacement therapy.

Materials and Methods: We retrospectively reviewed the records of hypogonadal men treated with testosterone replacement therapy and concomitant low dose human chorionic gonadotropin. Testosterone replacement consisted of daily topical gel or weekly intramuscular injection with intramuscular human chorionic gonadotropin (500 IU) every other day. Serum and free testosterone, estradiol, semen parameters and pregnancy rates were evaluated before and during therapy.

Results: A total of 26 men with a mean age of 35.9 years were included in the study. Mean followup was 6.2 months. Of the men 19 were treated with injectable testosterone and 7 were treated with transdermal gel. Mean serum hormone levels before vs during treatment were testosterone 207.2 vs 1,055.5 ng/dl ($p < 0.0001$), free testosterone 8.1 vs 20.4 pg/ml ($p = 0.02$) and estradiol 2.2 vs 3.7 pg/ml ($p = 0.11$). Pretreatment semen parameters were volume 2.9 ml, density 35.2 million per ml, motility 49.0% and forward progression 2.3. No differences in semen parameters were observed during greater than 1 year of followup. No impact on semen parameters was observed as a function of testosterone formulation. No patient became azoospermic during concomitant testosterone replacement and human chorionic gonadotropin therapy. Nine of 26 men contributed to pregnancy with the partner during followup.

Conclusions: Low dose human chorionic gonadotropin appears to maintain semen parameters in hypogonadal men on testosterone replacement therapy. Concurrent testosterone replacement and human chorionic gonadotropin use may preserve fertility in hypogonadal males who desire fertility preservation while on testosterone replacement therapy.

Key Words: testis; infertility, male; testosterone; chorionic gonadotropin; spermatogenesis

Abbreviations and Acronyms

E = estradiol

FP = forward progression

FT = free T

HCG = human chorionic gonadotropin

T = testosterone

TMS = total motile sperm

TRT = T replacement therapy

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Study received institutional review board approval.

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MALE hypogonadism is characterized by low serum T and characteristic symptoms, including fatigue, decreased libido, erectile dysfunction, difficulty concentrating, sleep disturbances and loss of lean body mass or weight gain. The prevalence of male hypogonadism is reported to be 37% in the United States and a higher prevalence is observed with increasing age.[1] The im-

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pact of T deficiency on the overall health of men was recently examined in meta-analyses.[2–4] Hypogonadism was found to be linked to cardiovascular mortality, metabolic syndrome, osteoporosis, frailty, noninsulin dependent diabetes and depression.

Treatment for hypogonadism typically includes TRT, which results in satisfactory amelioration of symptoms and normalization of serum T. However, treatment with exogenous T decreases serum gonadotropins, impairs normal spermatogenesis and suppresses intratesticular T. Azoospermia develops in up to 40% of patients on TRT and, as a result, treatment of hypogonadal men desiring to reproduce while on TRT remains a challenge.[5] However, recent studies indicate that intratesticular T can be maintained during TRT with co-administration of low dose HCG, suggesting that exogenous HCG in the setting of TRT may also preserve spermatogenesis in these men.[6] We hypothesized that HCG is protective and preserves spermatogenesis in patients undergoing TRT.

Table 1. *Patient demographics*

No. pts	26
Mean ± SD age	35.9 ± 9.5
Mean ± SD followup (mos)	6.2 ± 4.9
No. TRT formulation:	
Transdermal	7*
Injectable	19†
Mean ± SD pre-TRT hormone levels (ng/dl):	
T	207.2 ± 99.2
FT	8.1 ± 3.9
E	2.2 ± 1
Mean ± SD pre-TRT semen parameters:	
Semen vol (ml)	2.9 ± 1.4
Sperm density (million/ml)	35.2 ± 29
% Sperm motility	49 ± 10.4
Forward progression	2.3 ± 0.3
TMS (million)	84.6 ± 82.4
Mean ± SD post-TRT hormone levels (ng/dl):	
T	1,055.5 ± 420.9
FT	20.4 ± 13.5
E	3.7 ± 2.6

* AndroGel® (5 gm daily) in 2 patients and Testim® (5 gm daily) in 5.
† Testosterone enanthate (200 mg weekly) in 2 patients and testosterone cypionate (200 mg weekly) in 17.

MATERIALS AND METHODS

After obtaining institutional review board approval, we retrospectively reviewed the medical records of hypogonadal men who desired fertility preservation during TRT and presented to a single andrology clinic at Baylor College of Medicine between 2006 and 2010. We identified 26 men, who were included in the study. All men were started on TRT using daily transdermal gels or weekly intramuscular injections as well as simultaneously on intramuscular HCG (500 IU) every other day. The hypogonadism diagnosis was based on symptoms, including low libido, erectile dysfunction, low energy, poor concentration, inadvertent weight gain and sleep disturbances as well as serum T 300 ng/dl or less.

Baseline T, FT and E were assessed before the start of TRT, as were baseline semen analyses. Men were followed after TRT initiation approximately every 2 to 4 months. The effects of treatment on serum hormone values and serum parameters were assessed at followup. All serum hormone evaluations were performed at the Laboratory for Male Reproductive Research and Testing, Baylor College of Medicine on a single Access® 2 assay system.

Data were analyzed using Excel® and SPSS®. The study was powered to identify a 45% difference in any semen parameter with an α error probability of 20% and a total sample size of 24 patients required. Statistical comparisons between baseline and followup values were performed using the Student t test after evaluating our data set for parametricity using Q-Q plots and Kolmogorov-Smirnov goodness of fit testing. Statistical significance was considered at $p \leq 0.05$.

RESULTS

A total of 31 consecutive hypogonadal men who desired fertility preservation were identified for study inclusion. In 26 of these men complete data were available on semen parameters and serum hormone quantitation before and after TRT. The average ± SD age of our cohort was 35.9 ± 9.5 years. Men were followed a mean of 6.2 ± 4.9 months and up to 18 months (table 1). Of the men 19 men were treated with injectable T formulations, while 7 used transdermal gels. All men received intramuscular HCG (500 IU) every other day.

In the cohort mean serum hormone levels before vs during treatment were T 207.2 ± 99.2 vs 1,055.5 ± 420.9 ng/dl ($p < 0.0001$), FT 8.1 ± 3.9 vs 20.4 ± 13.5 ng/dl ($p = 0.02$) and E 2.2 ± 1.0 vs 3.7 ± 2.6 ng/dl ($p = 0.11$), supporting the efficacy of TRT in these men. Mean pretreatment semen parameters were volume 2.9 ± 1.4 ml, density 35.2 ± 29.6 million per ml, motility 49.0% ± 10.4%, FP 2.3 ± 0.3 and TMS count 84.6 ± 82.4 million.

To ascertain the effects of exogenous TRT and HCG on semen parameters the men were followed at 2 to 4-months intervals with semen parameters and hormonal assessment compared to pretreatment parameters. A statistically significant decrease in semen volume was observed at 1 to 2 months of followup ($p = 0.04$). This small difference was not observed at any other followup point. Furthermore, no statistically significant differences were noted in other semen parameters at any followup time (table 2). No significant differences were observed in semen parameters between the injectable and transdermal TRT groups (table 3). Taken together, these data indicate that concomitant HCG therapy in the setting of TRT is effective for preserving semen parameters.