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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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.

Table 2. *Mean pre-TRT and post-TRT semen analysis*

	Mean Pre-TRT	Mean Post-TRT (days) 0–60	60–120	120–180	180–360	Greater Than 360
Semen vol (million)	2.9	2.7	1.8	2.7	2.5	2.5
p Value		0.84	0.04	0.86	0.56	0.39
Density (million/ml)	35.2	22.9	20.7	32.9	35.6	30.2
p Value		0.13	0.15	0.77	0.98	0.61
% Motility	49	46.7	42.2	49.5	58	54.2
p Value		0.68	0.51	0.93	0.08	0.08
FP	2.3	2.3	2.7	2.4	2.5	2.3
p Value		0.9	0.05	0.62	0.1	0.96
TMS (million)	84.6	63.4	37.7	77.7	87.3	73.6
p Value		0.44	0.11	0.77	0.94	0.71

DISCUSSION

As life expectancy has increased in the last century, so has the prevalence of hypogonadism, which has important negative sequelae on the health of men. The prevalence of hypogonadism is within the 12% to 37% range in population based studies.[1,7] According to data from the Centers for Disease Control, 74% of men visit a physician office annually.[8] Extrapolating data from the United States Census and the reported prevalence of hypogonadism, approximately 14 million men 45 years old or older who visit a primary care physician office may have androgen deficiency.[1] Many of these men are interested in maintaining fertility. As a result, balancing the medical and fertility concerns of hypogonadal patients is a growing challenge for physicians.

Currently, the armamentarium for the medical treatment of male hypogonadism includes clomiphene citrate, anastrozole and exogenous T with the former 2 uses being off label. Clomiphene citrate, a selective estrogen receptor modulator, is effective for increasing serum T and safe in hypogonadal patients on long-term therapy.[9] Anastrazole, a potent aromatase inhibitor, increases serum T and bioavailable T, while decreasing E production.[10] While these 2 treatment options preserve the hypothalamic-pituitary-gonadal axis and spermatogenesis, minimal improvements in hypogonadal symptoms and lean body mass have been observed.[9,10]

Exogenous T induced decrements in semen parameters are well documented. Administering exogenous T in eugonadal men caused negative feedback in the hypothalamic-pituitary-gonadal axis and resulted in azoospermia or severe oligospermia (less than 5 million per ml) in 70% after 18 months of therapy.[11] Notably, TRT cessation only partially restored fertility in up to 85% of these men. Furthermore, TRT induced infertility is a growing phenomenon in the setting of continued abuse of anabolic steroids.[12] High dose HCG (3,000 IU every other day) has been used to successfully reverse exogenous T induced spermatogenic impairment, while low dose HCG has maintained intratesticular T levels during TRT, suggesting that it could also preserve semen parameters in men on TRT.[6,13]

Our data demonstrate that concomitant administration of low dose HCG in men on TRT preserves spermatogenesis. Not surprisingly, in our series pretreatment semen parameters were below the 50th percentile using 2010 WHO semen parameter criteria, given that our cohort comprised hypogonadal men.[14] None of the men in the cohort became azoospermic during treatment and no significant decrease in semen parameters was noted compared to pretreatment data at any point during followup. The protective effect of low dose HCG appears to be independent of the T formulation since no differences in semen parameters were found between the transdermal and injectable groups.

Our study is limited by several factors, including its retrospective nature, followup duration, small sample size and a lack of a control arm. A larger sample size might have enabled us to better compare the observed effect among the different T formulations. Furthermore, pregnancy information was incomplete in the cohort, in part because not all patients actively pursued pregnancy during the study period. Men were not queried regarding the timeline for achieving pregnancy and female fertility factors were not assessed for each couple. Further followup of our cohort will provide additional data on the pregnancy outcome associated with concomitant low dose HCG therapy in the setting of TRT.

To our knowledge this is the first report of fertility preservation in the setting of TRT with coadministration of low dose HCG. A future prospective study with longer followup, larger sample size and a proper control group is needed to validate the observed benefit of HCG and pregnancy outcomes.

Table 3. *Semen analysis in 7 patients with transdermal and 19 with injectable TRT*

TRT	Mean ± SD Sperm Count/Million Total	Motile	Mean ± SD % Motility	Mean ± SD FP
Before:				
Transdermal	35.5 ± 28.3	43.6 ± 70	42.2 ± 10.2	2.3 ± 0.1
Injectable	33.7 ± 38	49.8 ± 44	51.3 ± 10	2.4 ± 0.3
p Value	0.08	0.6	0.93	0.14
After:				
Transdermal	30.8 ± 15	37 ± 36	47 ± 20.7	2.7 ± 0.6
Injectable	30.6 ± 26.8	46.7 ± 39	51.3 ± 13	2.4 ± 0.3
p Value	0.99	0.64	0.68	0.22

CONCLUSIONS

Treatment for hypogonadal men who desire fertility preservation continues to be a challenge for physicians. Low dose HCG appears to protect and support continued spermatogenesis when given in conjunction with injectable or topical TRT.

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