Testosterone supplement based on hCG resulted in earlier masculinization and no inferior spermatogenesis compared to hCG alone in treatment of patients with idiopathic hypogonadotropic hypogonadism

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Introduction

Gonadotropin therapy is commonly used treatment to patients with male isolated hypogonadotropic hypogonadism (IHH) to induce virilization and spermatogenesis. 5.6-15.0% of male IHH patients showed poor responses to gonadotropin treatment, therefore testosterone (T) supplement can serve as an alternative therapy to help them normalize serum T levels and promote virilization. However, treatment with exogenous T impairs spermatogenesis and suppresses intratesticular T levels. Thus, this retrospective study aimed to determine whether oral testosterone undecanoate (TU) supplement based on human chorionic gonadotropin (hCG) would negatively impact spermatogenesis in IHH patients compared to hCG alone.

Methods

A total of 107 male IHH patients were recruited and were divided into group A (n=54) and group B (n=53) according to their voluntary choices. Group A received intramuscular hCG along with oral testosterone undecanoate (TU), while group B received hCG alone. In both groups, hCG was injected at an initial dosage of 2000IU twice per week. TU was maintained at a low dosage of 40mg bid. Patients were regularly followed up and their hCG dosages were adjusted to normalize serum T levels in the first 6 months. Subgroup analysis was performed based on the basal testicular volume (BTV) (≥ 4 ml and < 4 ml). SPSS version 23.0 was used for data analysis.

Results

The median follow-up time of both groups was 29 months.

1. Significant improvements were seen in Tanner stages, testicular volumes, hormone levels and semen parameters in both groups between pre- and post-treatment period ($P < 0.001$).
2. Compared to group B, the median time to achieve Pubic hair Tanner stage III, V and genital Tanner stage III, V was significantly shorter in group A ($P < 0.05$). Similarly, the median time to normalize serum T levels in group A was also significantly shorter ($P < 0.001$).
3. There were no significant differences in rate of spermatogenesis, sperm concentration, and the median time to achieve sperm concentration > 0×10^6 and 15×10^6 ml^{-1} between both groups.
4. In group A, compared to the basal testicular volume (BTV) < 4 ml subgroup, the BTV ≥ 4 ml subgroup had shorter median time to achieve sperm concentration > 0×10^6 ml^{-1}, shorter median time to achieve sperm concentration ≥15×10^6 ml^{-1} and a higher median sperm concentration. In group B, compared to the BTV < 4 ml subgroup, the BTV ≥ 4 ml subgroup had shorter median time to achieve sperm concentration ≥ 15×10^6 ml^{-1}.
5. No significant differences in side effects were observed between both groups, especially acne and gynecomastia.

Conclusion

Testosterone supplement based on hCG had no harmful impacts on spermatogenesis compared to hCG alone, and it shorten the time to normalize serum T levels and promote virilization.

Table 1: Clinical characteristics after treatment of IHH patients

	hCG/TU group (n = 54)	hCG group (n = 53)	P
Follow-up time (months), median (range)	29 (12-72)	29 (12-72)	0.311
hCG dosage adjustment, n (%)	15 (27.8%)	21 (39.6%)	0.195
Height (cm)	176.8±6.3	177.0±6.3	0.868
Pubic hair Tanner stage	4.8±0.6	4.4±1.0	0.011
Genital Tanner stage	4.9±0.2	4.5±0.8	0.001
Testicular volume (ml)	12.0±4.1	12.2±4.4	0.830
Therapeutic T (ng ml^{-1})	3.0±1.2	3.2±1.8	0.411
Spermatogenesis, n (%)	29 (53.7%)	28 (52.8%)	0.928
Sperm concentration ($\times10^6$ ml^{-1}), median (interquartile range)	15.6 (8.3-54.1)	15.7 (9.6-50.1)	0.917

Table 1. hCG dosage adjustment indicated rate of hCG dosage adjustment in each group. Median sperm concentration was calculated from patients with successful spermatogenesis. Analysis of genital Tanner stage and testicular volume excluded patients whose TV couldn't be measured.

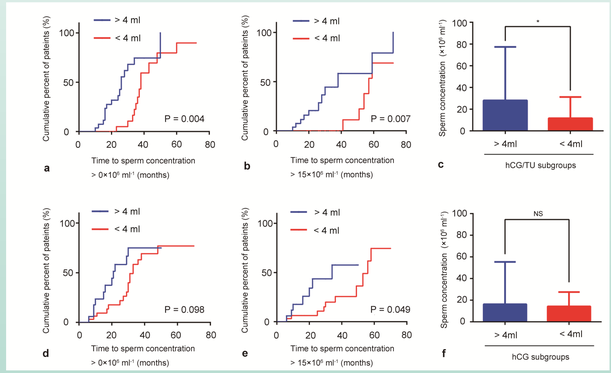

Figure 3: Follow-up time required to achieve different thresholds of semen concentration between subgroups with BTV ≥ 4 ml and < 4 ml. (Kaplan-Meier analysis).
(a) Cumulative percent of patients in the hCG/TU subgroups with BTV ≥ 4 ml (n=27) and < 4 ml (n=23) to achieve sperm concentration > 0×10^6 ml^{-1} (P = 0.004). (b) Cumulative percent of patients in the hCG/TU subgroups to achieve sperm concentration ≥ 15×10^6 ml^{-1} (P = 0.007). (c) Median sperm concentration with interquartile range in the hCG/TU subgroups (P = 0.047). (d) Cumulative percent of patients in the hCG subgroups with BTV ≥ 4 ml (n=17) and < 4 ml (n=32) to achieve sperm concentration > 0×10^6 ml^{-1} (P = 0.098). (e) Cumulative percent of patients in the hCG subgroups to achieve sperm concentration ≥ 15×10^6 ml^{-1} (P = 0.049). (c) Median sperm concentration with interquartile range in the hCG subgroups (P = 1.000).

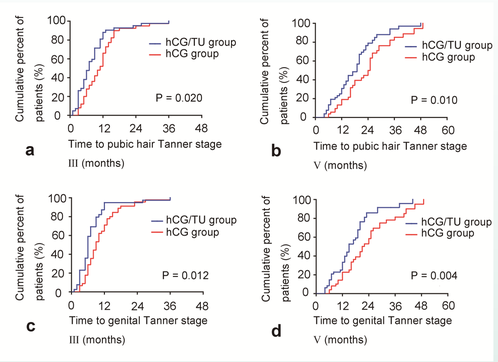

Figure 1: Follow-up time required to achieve different thresholds of Tanner stage (Kaplan-Meier analysis).
(a) Cumulative percent of patients in the hCG/TU group (n=42) and the hCG group (n=50) to achieve pubic hair Tanner stage III (P = 0.020). (b) Cumulative percent of patients in the hCG/TU group (n=52) and the hCG group (n=53) to achieve pubic hair Tanner stage V (P = 0.010). (c) Cumulative percent of patients in the hCG/TU group (n=39) and the hCG group (n=45) to achieve genital Tanner stage III (P = 0.012). (d) Cumulative percent of patients in the hCG/TU group (n=48) and the hCG group (n=49) to achieve genital Tanner stage V (P = 0.004).

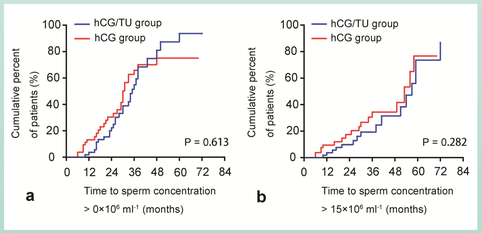

Figure 2: Follow-up time required to achieve different thresholds of semen concentration (Kaplan-Meier analysis).
(a) Cumulative percent of patients in the hCG/TU group (n=54) and the hCG group (n=53) to achieve sperm concentration > 0×10^6 ml^{-1} (P = 0.613). (b) Cumulative percent of patients in the 2 groups to achieve sperm concentration ≥ 15×10^6 ml^{-1} (P = 0.282).